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CONTENTS

1 **REMINISCENCES OF AN OLD-TIME DOCTOR** *George Blumer*

29 **EXPERIMENTAL CEREBRAL MUCORMYCOSIS IN RABBITS WITH ALLOXAN DIABETES** *Henry Bauer, John F. Flanagan, and Walter H. Sheldon*

57 **THE ARTERIAL PATTERN IN THE HAND** *Henry C. Bowering and David J. Morton*

76 **EXPERIMENTAL BACTEREMIA IN NORMAL AND IRRADIATED RATS I. II** *Hollingsworth and Paul B. Beeson*

93 **HEPATIC RADIOAUTOGRAPHY FOLLOWING INTRAVENOUS INJECTION OF RADIOACTIVE CHROMIUM PHOSPHATE AS A FURTHER CONTRIBUTION TO RETICULOENDOTHELIAL FUNCTIONAL TESTS** *Horace B. Gabriels, Duncan Coulter, Jr., and John F. Cutler*

123 **BOOK REVIEWS**

THE YALE JOURNAL
OF BIOLOGY AND MEDICINE

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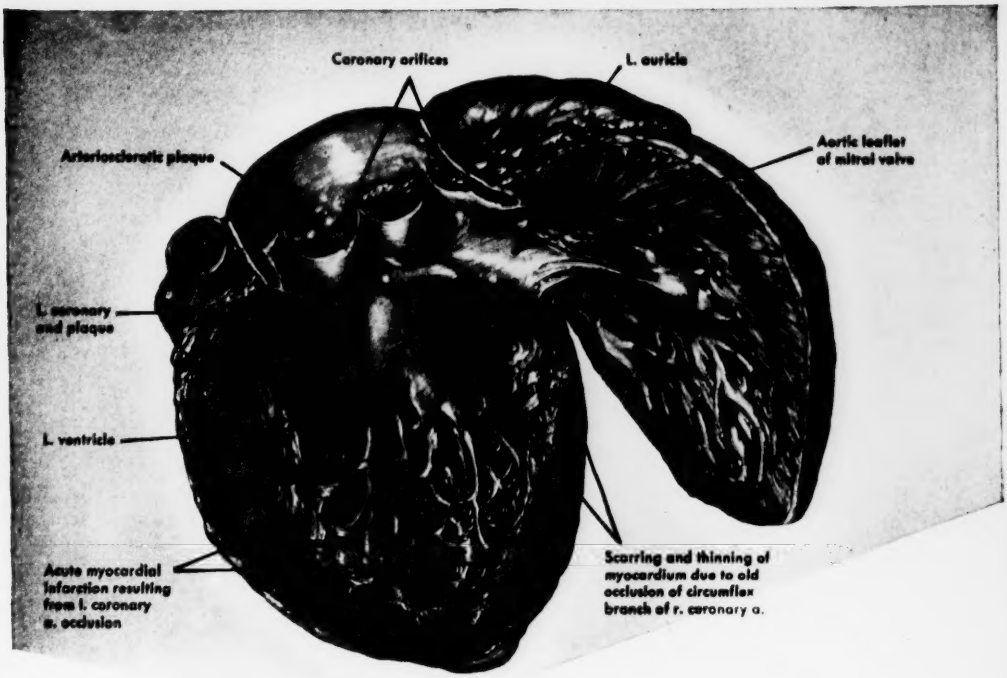
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"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

References:

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996 on E

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Dental chap came in with a live hamster for help in photographing its molars, and when that was done, he asked what's new in photomicrography. We told him about Julius Rheinberg's papers in the *Journal of the Quekett Microscopical Club* for April and November, 1897. Some beautiful Ektachrome photomicrographs of tooth structure have come out of this.

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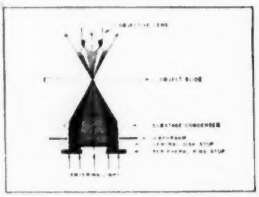

disk just fills the aperture of the objective while the peripheral zone provides light for the object to refract, then one sees things like a red paramecium swimming in a green pool, or vice versa as fancy and good seeing may dictate. Of course, this doesn't work with high-powered objectives that take all the available aperture of the condenser to fill them, in which case you had better look into phase microscopy after all.

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REMINISCENCES OF AN OLD-TIME DOCTOR

Quick, thy tablets, memory.

Matthew Arnold

I. MEDICAL EDUCATION IN THE GAY NINETIES

Early in June 1889 the writer entered Cooper Medical College, San Francisco, now the Medical Department of Stanford University. Prior to his admission he had, under the tutelage of a friend, Dr. Charles Pemberton Murray, a graduate of Columbia's College of Physicians and Surgeons, been quizzed twice a week for about a year on assigned readings from Gray's Anatomy and Dalton's Physiology, at that time standard texts. He was therefore better prepared than most entering students, and that may have been the reason why Dean Henry Gibbons, Jr. permitted him to enter at the age of seventeen, though the college catalogue definitely stated that no one under the age of eighteen would be allowed to matriculate.

The course at Cooper Medical College, as was then the case in many American medical schools, extended over three years and, on account of the peculiar summer climate of San Francisco with its morning high fog and its afternoon cool breezes permitting dissection all through the summer, began early in June and ended in December. Third year students had to take also a spring term of three or four months preceding the regular summer term. Very few of the students were college graduates, most of them entered on high school diplomas, though they could be admitted after an examination conducted by the college authorities. On this account the range in age between the youngest and oldest students was usually much greater than at present. Occasionally students in their forties or even their fifties, who had decided to study medicine comparatively late in life or who perhaps had spent years saving enough cash to pay for their medical education, were mixed in with much younger men. The college was co-educational and in my class of about forty there were two women.

The methods of instruction were largely didactic, though the college controlled medical, surgical, and obstetrical wards in the City and County Hospital out in the Potrero (more than an hour's ride on streetcars from

*Formerly John Slade Ely Professor of Medicine, Yale University School of Medicine

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the Medical School) and also had its own Dispensary in the modern Medical School building. The only real laboratory courses were dissection and a course in *clinical chemistry* given by Professor Johnson, a rubicund and humorous individual and a good teacher who trained us mainly in the chemistry of urine. I recall that prior to his final examination he announced "anyone who spells pus with two esses will be plucked."

Anatomy, as was common then in most American medical schools, was taught by a surgeon, for this was before the days of full-time preclinical teachers in most of them. Dr. Plummer, the professor, was a large, bearded man, with a sense of humor who, judging from his lectures, knew Gray's Anatomy by heart. His talks were given in a large amphitheatre, and when an occasional student fell asleep during his discourse he stopped abruptly and recited an appropriate poem, the opening words of which were "Oh sleep." Dissection was under Dr. Charles Farnum, widely read in anatomy and greatly respected by the students. The dissecting material was well prepared and students paid so much for each "part." Each cadaver was divided into two uppers, two lowers, and the head. I think the dissection of the head was shared by two students and I remember one female cadaver who had so many gold filled teeth that the students who owned the head removed them and sold the gold for enough to pay for it. We had a good many Polynesian cadavers, many of them men of magnificent physique, and I suspect that they had been sailors who died in charity hospitals in San Francisco and who were turned over to the Medical School because they were unclaimed.

We had lectures on *histology* from Dr. Joseph Wythe, a very short and kindly ex-minister who had gone into medicine. In the lecture hall most commonly used, the lecturers spoke from a long platform which stretched across the back of the hall. Upon this was a long, flat-topped table on which a movable stand for notes could be placed. After Dr. Wythe's lectures a row of microscopes was placed on this and the class moved along in Indian file peering into each microscope for a minute or so at stained sections which illustrated the subject of the lecture. I was accustomed to looking through a microscope as my father owned one, but I wondered how much some of the class absorbed from this exercise.

Strangely enough *physiology* was taught by a genito-urinary surgeon, C. N. Ellinwood, a former pupil of the famous American-born Phillippe Ricord, who practised as a specialist in venereal diseases in Paris during most of his professional career. The instruction was purely didactic as there was no physiological laboratory and the chief impression of the lectures which I carried away was the constant repetition of the word *metabolism*

which Dr. Ellinwood loved to roll out sonorously. The doctor also directed the venereal clinic in the Dispensary and it was a sight to see him pass a metal sound with one hand after he had inserted it into the meatus; he was dexterity personified.

Physiological chemistry and *pharmacology* were not at that time taught at Cooper Medical College. What little *chemistry* we got was from Professor Johnson's course already mentioned. We doubtless absorbed some *pharmacology* from the lectures of Professor Charles Steele, the Professor of *therapeutics*, a kindly and handsome gentleman, medium-sized and dark, and a good lecturer.

Pathology was taught by Dr. Albert Abrams in a room off the College Museum, his lectures being based on museum specimens which were temporarily removed from the cases to serve as illustrations for his discourses. Abrams was a brilliant young man, a graduate of the University of Heidelberg, and an excellent lecturer. Later in life he developed certain mental quirks which will be described in the section on the interne years.

There was no course in *bacteriology* and the only experience with that subject that I acquired, along with a section of the class, occurred by chance. We were leaving the French Hospital one day when a young surgeon, Dudley Tait, who had recently returned from study in Paris, met us near the exit and showed us a culture of the anthrax bacillus from a patient then in the hospital with a malignant carbuncle.

Our training in *physical diagnosis* was practical and was supervised by Dr. George W. Fuller. The exercises were conducted in Dispensary rooms not in use, and the men in the class stripped to the waist and practised on each other. We obtained further practice on our patients in the medical wards of the City and County Hospital.

In the clinical branches the formal course in *medicine* was given by an Englishman, Dr. S. O. L. Potter who, despite a slight impediment in speech, presented his subject clearly and succinctly. He was the author of an excellent textbook on therapeutics. In *clinical medicine* we were lucky to have as a teacher Joseph Oakland Hirschfelder, whose middle name was bestowed on him because he was the first white child born in the city of Oakland. He was a graduate of the University of Leipzig and his clinics were given at the bedside in the medical ward of the City and County Hospital, the students sitting in a semicircle around the bed of the patient used as a text. Furthermore, each senior student was assigned a ward bed and was required to take the history of each patient occupying it and to make progress notes. I happened to have a patient with chronic disease, a man with tabes dorsalis and a thoracic aneurysm, and he was not moved all

through the teaching period. There were few American medical schools at that time in which the students enjoyed such opportunities.

In *surgery* the formal lectures were given by Dr. Levi Cooper Lane, President of the College and nephew of its founder, Elias Cooper. He was a learned Missourian who was said to enjoy reading books in the original Latin and who himself wrote a textbook on surgery. His lectures were instructive and well delivered and he used to have small sections of the class go down to his office to witness minor operations on ambulatory patients. The subject of the first operation which I saw him perform was a woman with an epithelioma of the skin of the neck. Dr. Lane removed it very rapidly, without an anesthetic, with a forceps and a few snips of a pair of curved scissors. The woman stood it like a Trojan, but I had to make a hasty exit into the open air. However, after this one experience I had no further trouble watching operations, of which we saw many major ones in the surgical amphitheater at the City and County Hospital. At these operations most of the surgeons used aseptic precautions although there were one or two among the older men who did not believe in Lister's principles. I recall seeing such a surgeon do a major operation for abscess of the liver in an ancient Prince Albert coat liberally spotted with dried blood and pus.

The Dispensary clinics in surgery were particularly stimulating on account of an unusually acute teacher, "Johnny" Morse. As a junior student I wandered into the Surgical Clinic one day and saw him call up the seniors one by one to pass judgment on a small round tumor on a man's forehead. Most of them diagnosed lipoma or fibroma. Finally Dr. Morse turned to the patient and said, "when were you shot?" The man replied that he had been duck shooting with a careless friend, one of whose scattered pellets struck him on the forehead. Dr. Morse had noticed a tiny scar over the supposed tumor and from that and the size of the little mass had made the diagnosis.

In *obstetrics* Henry Gibbons, Jr., the Dean and a courtly gentleman, gave the formal lectures at the college. The students had no practical experience before graduation. Instruction in *gynecology* was given by Clinton Cushing, a lucid lecturer who always appeared in a full-dress suit with tails and a white tie. He used to invite small groups of senior students to witness his operations at the French Hospital. He was meticulous in his technique, which was the rigid asepsis of the English surgeon Lawson Tait rather than the original Listerian method.

The lectures in *pediatrics* were given by an attractive, sandy-haired, young doctor not many years out of medical school, William Fitch Cheney. He was an excellent teacher and a great favorite of the students.

The teacher in the *specialties* who made the greatest impression on me was Adolf Barkan, an ophthalmologist and otologist trained in Vienna. He had a fine personality, marked teaching ability, and a profound knowledge of his subject. I recall going one morning into his clinic with a bad cold and asking one of the assistants, on the advice of one of my chums, to swab out my nose with a solution of a new drug, cocaine. A strong solution must have been used for my friend and I set out for the City and County Hospital on the streetcar and I, not usually very loquacious, nearly talked him to death. I have a vivid recollection of the profound mental depression which ensued when the effects of the drug wore off and I was never tempted to try it again.

Our only experience with *psychiatry* was a day at the State Hospital for the Insane at Stockton. The class took a stern wheeler up the river the night before, arriving at Stockton early the next morning. At the hospital Dr. Hoisholt spent most of the day presenting patients who suffered from feeblemindedness, epilepsy, and the different forms of insanity. Two groups of patients made a great impression on me: (i) A number of cretins, and (ii) among the epileptics a young man with so-called cursive epilepsy. When he had an attack he ran for the nearest horse, jumped on its back, and rode it at top speed until the attack subsided. He must have lived on a ranch, perhaps a cattle ranch, to be able to go through this performance. It was evidently cursive epilepsy wild western style.

I should say that, everything considered, the medical education we received at Cooper Medical College was sound so far as it went, but at that time it naturally did not include preliminary training in chemistry, biology, and physics of the type now required for entrance to a medical school. It is only fair to state that we did have among our teachers many with the stimulating personality which is so essential to successful education.

II. THE INTERNE YEARS

> The love of Medicine makes the scientist, the love of the patient makes the physician.
>
> French saying quoted by Archibald Malloch

When I graduated with my class in December 1891 I was given a certificate with the assurance that I would get my diploma when I reached the age of twenty-one. I was also appointed an externe at the City and County Hospital, beginning January 1, 1892, but a man who had received an interne appointment having dropped out within a few weeks, I was appointed interne in his place. The service was a rotating one, as was usual

at that time, and I began in the Medical Service of which Joseph O. Hirschfelder was Chief. We took histories of the patients in the beds assigned to us, and Dr. Hirschfelder made daily rounds and discussed each case though I do not recall that he actually dictated notes. However, we got a great deal of information out of his discussions, founded on long experience and extensive study of the literature, especially of medical journals published in English and German.

About the only laboratory work done at that time was urine examination, chemical tests for albumen and sugar, and microscopic tests for casts, etc., etc. We had very interesting patients with all sorts of diseases both acute and chronic. There were patients of many nationalities, for San Francisco in those days had a large French colony, an extensive Chinatown, and, as an important seaport, men of all nations were apt to show up though there was a Marine Hospital for sailors which probably was often overcrowded. I do not recall any isolation ward in the old wooden City and County Hospital of 1892, but there was a so-called Pest House in the Potrero Hills about a mile or so from the main hospital and for some time it was one of my duties to walk over there once a week and dress those lepers who had open sores. There were about 30 lepers over there, most of them with the tubercular form of the disease, though I remember one young girl, a Scandinavian, who had the anesthetic type. This experience stood me in good stead, for years later in New Haven I recognized four or five cases of leprosy, one of them in a man who worked in a restaurant, another in a Spanish War veteran who had been in the Philippines.

At one time when Albert Abrams was substituting for Dr. Hirschfelder, Frank Griffin, Frank Fischer, and myself were making rounds with him. We came to the bedside of a German patient who could speak no English. Dr. Abrams remarked that he thought hypnosis might benefit the man and that he would hypnotize him and tell him that a book on the bedside table was an apple and that he was to take a bite out of it. He proceeded to make some passes over the man and then told him in German that the book was an apple and to take a bite. The man rather sheepishly picked up the book and took a half-hearted bite. After Abrams left, Frank Fischer, a good German scholar, told us that Abrams had said "Essen Sie das Buch" not "Essen Sie der Apfel." The later history of Abrams, with his fake diagnostic machines, is still well known to many of the profession. Indeed, some quacks are still advertising and using machines which closely imitate it.

In the men's surgical ward there were no women nurses, only a "dresser," Jack Campbell, a friendly and kindly soul. In the winter time a lot of hoboes with badly infected legs turned up in order to get free lodging

during the rainy season. They were often so lousy that Jack took them into the bathroom at the far end of the ward and turned the hose on them. It was rumored that many of them produced the infection by scrubbing their leg with a brick contaminated with horse manure. They commonly had a severe and serious deep cellulitis needing multiple incisions. Some of them died of sepsis. We called these legs "whiskey legs," and no doubt many of these patients were chronic alcoholics. Dr. Stanley Stillman, an excellent surgeon, was our chief instructor. He taught us how to prepare patients for operations, at which we assisted him, and we picked up many valuable points from him. The service was an active one and covered all types of surgical disease, both traumatic and pathological. In the women's ward there were, of course, women nurses. I recall going in there one day to take the history of an old Irish woman. She looked me over and said, "Who are you? I want to see the doctor."

The *obstetrical* experience was limited. I do not think either of the regular schools, Cooper and Toland, or the Homeopathic School controlled the ward. Internes were assigned there for a period of two or three weeks and attended the patients who were delivered during their period of service. The Hospital had one experienced, permanent resident physician, Dr. Arthur Mays, and he could be called on for help if needed. I remember that he was strongly opposed to what he called "meddlesome midwifery." Luckily I had no complicated cases.

The internes' quarters in the hospital were comfortable. Frank Griffin, Dick Gibson, and I had a very large room with three single beds in the Administration Section. There was a billiard table in an adjacent room and there was a good tennis court on the hospital grounds. The food was good, well cooked and appetizing, but rather monotonous. Mutton being very cheap, we had it almost every day. We had plenty of milk. On Christmas Day the pharmacist brewed a milk punch as an accessory to the main meal that had quite a kick to it. Relations between the internes from the different schools were amicable though we had no formal social or medical meetings. It was a satisfactory year in most ways and I returned home January 1, 1893, well satisfied with the experience.

When I reached home I found that my father had been corresponding with my cousin, Dr. G. Alder Blumer, then Superintendent of the State Hospital for the Insane at Utica, New York. As I was still nearly three months short of 21 years of age, he had suggested that I be sent to Baltimore since the Johns Hopkins Hospital had graduate courses beginning early in the year and lasting until May 1st. The Superintendent of the Hospital, Dr. Henry Mills Hurd, formerly a psychiatrist, was an old friend

of my cousin. So some time in late January or early February I arrived in Baltimore and got lodgings within two or three blocks of the Hopkins Hospital. There was thus a hiatus of about four months between my first and second internships. During this period I took the graduate courses in pathology and bacteriology.

Once my friend Dr. Murray said during our quiz sessions that if I ever got a chance to work with William H. Welch, I should not fail to grasp it. The graduate course in pathology at Hopkins was naturally under him as he was Professor of Pathology. There were, I think, three afternoon sessions a week; first a lecture, sometimes given by Dr. Welch, sometimes by his associate, Dr. Simon Flexner, and sometimes by the Fellow in Pathology, Llewellys F. Barker. This was followed by a study of sections stained with hemotoxylin and eosin which were handed out already cut but were stained by the students themselves. These sections illustrated the subject of the lecture. The two assistants did elbow teaching while the students were studying the specimens, helping them to identify lesions concerning which they were in doubt. As is well known, Dr. Simon Flexner subsequently became Professor of Pathology at the University of Pennsylvania and finally Director of the Rockefeller Institute for Medical Research, and Dr. Barker became Professor of Anatomy at the University of Chicago and finally returned to Hopkins as a Professor of Medicine. Needless to say, all were good lecturers and thoroughly grounded in the subject. The students, each with a microscope, sat on stools ranged along laboratory tables. Next to me on the left was a lanky, sandy-haired doctor in the uniform of the Army Medical Corps. I spoke to him the first day and immediately discovered from his accent that he was English. His name was James Carroll and he later became famous with Drs. Reed, Lazear, and Agramonte as one of the group, the *Men in White*, who studied yellow fever in Cuba. Dr. Walter Reed also happened to be working with Dr. Welch at this time. He was doing an *arbeit* on the liver lesions of typhoid fever, which disease was then very prevalent all over the country and one of the scourges of armies. In fact, there were quite a few Army doctors studying pathology or bacteriology, for the men in the Army Medical Corps had to pass an examination before being advanced in rank.

The course in bacteriology occurred on alternate afternoons to that in pathology and was given by Dr. George H. F. Nuttall, who soon, however, left to take a position in Cambridge University, England, and was succeeded by Dr. Meade Bolton, a genial southern gentleman. This course, too, was a practical one. The students were taught to make, standardize, and sterilize their own media and were given cultures of the common bac-

THREE DEANS OF THE YALE UNIVERSITY SCHOOL OF MEDICINE

Stanhope Bayne-Jones, 1935-1940; Milton C. Winternitz, 1920-1935; George Blumer, 1910-1920

(Photograph taken by Dr. Paul E. Rekers when a House Officer in the Department of Surgery.)

teria, beginning with harmless saprophytes and ending with the common parasites then known. These they had to stain with appropriate dyes, including Gram's stain, and they also had to study their growth on the common media then in use: bouillion, gelatin, agar, and potato. They were taught how to inoculate rabbits and guinea pigs. Since I had had neither laboratory pathology nor bacteriology in medical school, I profited greatly by both courses which were accompanied by readings from standard textbooks on the subjects.

As both pathology and bacteriology were given in the afternoon, the mornings were free and I filled in this time working in the Surgical Dispensary under John M. T. Finney and John Hobach. Dr. Finney was Dr. Halsted's chief assistant and took his place in the hospital when "the Professor" was away. He was an old football player, Princeton and Harvard, for in those days Harvard Medical students could play on the varsity team. He was also a fine surgeon, kindly and considerate to his patients and to his staff. I remember one of his quotations from his old Harvard Medical School teacher, John Homans: "No examination is complete without a sound in the bladder and a finger in the rectum." John Hobach was a surgeon to the Pennsylvania Railroad and a competent and kindly doctor. He told us that the railroad still required that all diagnoses be written in Latin. The work in the Surgical Dispensary was of course minor surgery but it gave an insight into the methods and technique then in use on Dr. Halsted's service. We were required to take careful histories and to record physical findings, and the training under two experienced surgeons was most valuable.

Toward the end of the graduate course Professor W. S. Halsted, head of the Department of Surgery, sent for me and asked me if I would like to join his interne staff for a year beginning May 1, 1893. While I had no itch to become a surgeon, I gladly accepted his invitation. The Johns Hopkins Medical School did not start until the fall of 1893 and it was necessary to pick up internes here and there until the time when the Hopkins Medical School began turning out its own graduates in 1897. It happened that in May 1893 the entire junior staff of the surgical department changed. The resident surgeon, who was the only salaried man, was Joseph Colt Bloodgood, "Bloodclot" to the staff. He was a graduate of the University of Pennsylvania who had formerly been on the junior surgical staff and was returning after study in Europe. The internes were Berwick Bruce Lanier, a nephew of the Southern poet, Chauncey Pelton Smith, also a Pennsylvania graduate, from Buffalo, New York, and myself. After they had got to know us, the nurses nicknamed us "the World, the Flesh, and the Devil,"

though I never knew which was which. We each had charge of a ward, or part of one, for there was one mixed Medical and Surgical Ward, D. Our duties were to take histories, make physical examinations, and enter a diagnosis on the record—we didn't call them "impressions" then. When the Professor, as Dr. Halsted was called, wished to make early rounds, we accompanied him and noted any of his observations on the patient's histories. In addition, we had other duties in the operating room, the accident room, and the pathological laboratory. In the operating room I spent six months as anesthetist, for this was before the days of specialization in anesthesia. The apparatus was rudimentary: a cone made out of an ordinary huckaback towel containing between its layers some stiff paper to prevent it from collapsing. In the apex of the cone, which fitted over the patient's nose and mouth, was a wad of absorbent cotton, and the etherizer had an ordinary ether can whose metal covered top had been punctured so that it allowed the escape of the ether drop by drop. The patient was told to breathe deeply and ether was added a few drops at a time as needed. There were legends regarding a former eccentric etherizer who always tucked a periosteal elevator into his blue denim overalls to pry open the patient's jaws if they became set and who sometimes pried out a few teeth. Dr. Halsted always watched the reaction of the patient to the anesthetic very carefully. It was rumored that one morning the eccentric etherizer was giving the anesthetic and gazing round the room. The patient was not breathing well. Dr. Halsted is said to have asked the anesthetist: "Has the patient stopped breathing, doctor?" The anesthetist replied "Not quite, sir, not quite," to which remark Dr. Halsted, who never raised his voice in anger, replied in icy tones: "The doctor is sarcastic this morning."

After six months of etherizing I was promoted to the job of handing instruments to the operator, who would usually say in a low voice: "Clamp," "ligature," "needle," or whatever he happened to need. The instruments were kept in a large glass dish containing a solution of carbolic acid and the man who handed instruments had therefore to wear rubber gloves to protect his skin. This was before Dr. Halsted introduced the use of rubber gloves for all the operating team, nor do I recall that they wore masks or white caps. All members of the operating team except the anesthetist wore short-sleeved white shirts and white trousers which were donned before and discarded after operations were over for the morning. The preoperative technique consisted in thorough scrubbing of the hands with green soap, immersion of the arms up to just above the elbows in a long glass dish of a saturated solution of permanganate of potash, decolorization in a saturated solution of oxalic acid, and finally soaking in a solution of bichloride of

mercury, 1 to 1000, for ten minutes. After that the team usually stood with their hands in the air until the field of operation had been rigidly cleaned and its vicinity had been covered with sterilized towels. No one of the team could touch anything that had not been sterilized after this performance and I remember once, when handing instruments for Dr. Finney, that I dropped a pair of forceps and involuntarily started to bend over to pick them up. Dr. Finney quickly reminded me that they were no longer sterile and I left them to be picked up by a nurse who was not part of the team. You could always tell a surgeon who had gone through this technique by his black finger nails, presumably due to the action of the mercury on the sulphur in the nails. Dr. Halsted had no illusions as to the sterilizing capacity of this technique. He knew perfectly well that the staphylococcus albus, residing in the ducts of the sweat and sebaceous glands was not destroyed, and yet during my year on the surgical staff I can recall but one clean case in which a wound became infected. Of course the technique was tough on those of the surgical teams who had tender skins and it sometimes caused dermatitis. Even this might possibly have been due to an unusually virulent staphylococcus albus or an unusually susceptible patient. In later years I reported as a bacteriologist a fatal case of sepsis due to this germ.

The accident room work at night fell to my lot, just why I do not remember. I had to get up two or three nights a week and go down to the accident room in the Dispensary. If a patient was suffering from something that I felt was serious, I called up Joe Bloodgood on the telephone and he came down and decided what was to be done. Luckily I have always been a good sleeper and could drop off very quickly after I had been up for an emergency. However, I did lose fourteen pounds during the year but put it back in two weeks during a vacation in the Adirondacks.

After the morning operations were over and we had eaten lunch, Dr. Bloodgood and I repaired to the pathological laboratory to describe the specimens removed that morning. Usually Joe Bloodgood dictated a description which I wrote in a book kept for that purpose. However, being resident surgeon, he was often called away to attend to emergencies and much of this work fell on my shoulders. I prepared sections for hardening and later cut and stained them. A description of the microscopic findings was entered in the book by either Dr. Bloodgood or myself. It was a most valuable training in surgical pathology and stood me in good stead in later years in Albany.

The surgery at the Johns Hopkins Hospital was mostly pathological rather than traumatic. This was before the days of automobiles and the hospital was quite a distance from the center of Baltimore and from the rail-

roads and the waterfront where severe accidents were likely to occur. The surgical internes saw a great deal of the diseases in which "the Professor" was especially interested: hernia, cancer of the breast, thyroid disease, and some diseases which were common among the population such as tuberculous cervical nodes, appendicitis, and various kinds of neoplasms. Dr. Halsted's interest in surgical technique led in my time to experiments with various ductile metals which might be used as sutures in the place of silk thread, which he preferred to catgut. Experimental work on the bactericidal effects of various metals was carried out by Meade Bolton. He would appear in the operating room between operations with Petri dishes of medium infected with staphylococci in the center of which was a disc of silver or copper or some other suitable metal. If an area of nongrowth appeared around the disc of metal, it obviously was bactericidal. The choice finally narrowed down to silver or copper, but the latter in practical tests, used as a foil over wounds, proved to be too corrosive and Dr. Halsted began using silver wire for continuous intracutaneous skin sutures and silver foil as a dressing immediately on the sutured wound.

There were certain points in techniques upon which "the Professor" insisted: (i) rigid control of hemorrhage to avoid shock, (ii) as little trauma to tissue as was possible, and (iii) in suitable cases, healing under a moist blood clot. To comply with these requirements necessitated the use of many clamps, some of them the small "mosquito" type devised by Halsted himself, great care in tying off vessels to avoid including too much tissue, and slow operation. Before studying out the technique Dr. Halsted had been a rapid operator. Some small vessels were not tied off but bleeding was controlled by torsion.

It is, of course, well known that Dr. Halsted originated the use of cocaine for local anesthesia by intracutaneous injection and nerve block. The experiments necessary to perfect the technique were done on himself, for at that time (1885) cocaine was not known to be a habit forming drug. Dr. Halsted, as is described in W. G. Macallum's Life, contracted the habit. He came to Baltimore and, aided by his old friend William H. Welch, overcame it. In spite of this there have been rumors that he did not conquer it. A year's observation of him as one of his assistants led me to the conclusion that at no time did he show the slightest sign of drug habituation. Indeed, he was perfectly frank on one occasion when I assisted him alone in the operating room in a minor operation under cocaine anesthesia on an old gentleman. As he injected the solution he said to the patient, "Now this will not hurt you much, I know for I have done it scores of times on myself."

My term of service with Dr. Halsted ended May 1, 1894, and before that time Dr. Osler, "the Chief" as the boys called him, had asked me to join his staff and do laboratory work, such as blood cultures and other bacteriological tests. The regular house staff still did the routine examinations of blood, sputum, urine and feces, and gastric-juice analysis. As a matter of fact, I always had some ward work too, for the laboratory work was not enough to keep me busy. William Sydney Thayer, a Harvard graduate and an outstanding clinician, was the resident physician. He had studied in Europe and was trained in the modern methods of blood examination. He and John Hewetson were gathering material for their book on malarial fever which was published a few years later. We had many patients with malaria on the wards, mainly from the region near Baltimore but occasionally from more distant parts of the South. There was no quartan fever in the Chesapeake Bay area but we occasionally got cases from the deeper South. It was a rule at that time that the blood of each malarial patient must be examined by the house officer responsible three or four times a day and a note on the findings at each examination had to be entered on the history. At that time the eosin and methylene blue stains of Wright and Hastings had not been introduced, and Ehrlich's triacid stain, which we used for routine blood work, was not satisfactory for the demonstration of the plasmodias. So we used unstained films made by placing a coverglass on a drop of the patient's blood collected on a slide. If the glassware was meticulously clean, the blood spread easily, usually as a single layer of cells. It was not hard to detect the intracellular parasites of tertian or quartan malaria because they were pigmented, and the same was true of the extracellular crescents and ovoids of the estivo-autumnal form. The young, intracellular, estivo-autumnal parasites were much more difficult to detect, but we had a great deal of practice and became quite expert. Dr. Thayer asked me to study the changes in malarial parasites in leeches, which I did for several months. A leech would be allowed to gorge itself on the blood of a patient with malaria, and I learned how gently to milk the leeches every day and get a little blood for examination and observation of the plasmodia under the microscope. There is a brief note on this work in Thayer and Hewetson's book. Dr. Thayer was a very keen clinician. I saw him make a diagnosis of coronary thrombosis, confirmed by autopsy, as early as 1896 – long before the syndrome was first identified in 1910. No doubt he got information on the diagnosis of coronary occlusion from Dr. Osler, for my friend Alvin Foord of Pasadena gave me a copy of a letter from George Dock, which showed that he, when on Osler's staff, and Dr. Osler had recognized a case during life in 1888 but had never reported it. In a patient on the medical

service with gonorrheal septicemia and endocarditis I was able to isolate the gonococcus from the blood during life by the method of Suttmann, and the finding was confirmed at autopsy. [This case was described by Dr. Thayer and myself in the *Archives des Médecine Experimentale* for November 1895 and, so far as we could determine from a study of the literature, was the first instance of the isolation of the gonococcus during life from the blood of a patient with gonorrheal septicemia.

The other members of the medical staff beside Drs. Thayer and Hewetson were Arthur Oppenheimer, a brilliant young Pennsylvania graduate who died an untimely death from a rare complication of typhoid fever, and two Canadians: Theodore Coleman and Christopher Carroll, the latter nicknamed "Christmas" Carroll. After Dr. Oppenheimer's death, Crosby Whitman, trained in Paris, joined the group. We were a harmonious crew and got along well together.

"The Chief" was generally acknowledged to be the leading clinician of his time. The details of his career can be found in Harvey Cushing's monumental biography. He was a dark, medium sized man of Cornish descent, an indefatigable worker, with a keen and somewhat puckish sense of humor, and an intense personal interest in his patients, his students, and his staff. He once remarked that human beings could be divided into the larks, who did their best work early in the day, and the owls, who did their best work at night. He was a lark himself and planned his time most carefully. He was a stickler for punctuality, at that time regarded as a virtue, and on the menu card of a dinner given to him before a trip to Europe in 1903 was a quotation from his own writings: "Promptness is the one quality in a physician necessary for success." Most of us present at this dinner passed around our menus to be autographed by Dr. Osler and the other guests. On my menu* and probably on others, he signed "Edgerton Y. Davis, Jr.," and thereby hangs a tale. During his Montreal days the Chief had written a series of fictitious but often plausible reports under that pseudonym. He claimed that Egerton Yorick Davis, Jr., was a real person, a retired American Army surgeon, but before Dr. Osler left Montreal to become a professor at the University of Pennsylvania, Davis was reported to have been drowned in the rapids of the Saint Lawrence River.

Working in Dr. Osler's clinic was an education not only in medicine but also in the psychology of handling patients. He was a learned man of great personal charm and he exemplified a dictum of Dr. Francis Peabody: "The secret of the care of the patient is in caring for the patient." At that time

* See illustration in *Arch. Int. Med.*, 1949, *84*, 39.

there was no separate pediatric service in the Johns Hopkins Hospital and it was a treat to see the Chief gain the confidence of the children under his care. He often greeted them with a smile and the remark: "Well! are you feeling nice and fat today?" His handling of adults often took the form of some whimsical remark at the beginning of his first interview which put the patient at ease and showed that he was not a pompous "stuffed-shirt." In his wards the beds were high enough so that an examiner could sit on a chair and get his knees under the frame. He never gave the impression of being hurried, but he always insisted that the interne in charge of a patient should have the history completed when he made rounds, which began promptly at 9 a.m. It was interesting to see the trail of internes, students, and visiting doctors who followed him as he led the procession, usually accompanied by Dr. Thayer, along the corridors and through the entrances to the wards. I can recall once hearing a convalescent patient, who was sitting outside of Ward D on the sun roof of the corridor, call out, "They're off at the Gut, they're off at the Gut"—the Gut no doubt being Guttenberg, then a favorite racetrack. In making rounds Dr. Osler would stop at each bed, for old patients often merely making a brief progress note. With new patients he usually sat at the bedside where he could examine the patient, listen to the history and laboratory reports, and then, carefully analyzing the findings, would dictate a note on the diagnosis and treatment. The prognosis was not, I think, discussed before the patient even in technical language. Some patients were ordered transferred to the surgical or gynecological services. We had occasional distinguished visitors on rounds and I well remember when Dr. Edwin Klebs, co discoverer with Loffler of the diphtheria bacillus, made rounds with us.

Dr. Osler was often described in those days of polypharmacy as a "therapeutic nihilist," but he was far from that. He usually prescribed well-known and long-tried remedies in adequate doses. He seldom used combinations of drugs. This was long before the days of psychosomatic medicine but no doubt much of the Chief's success lay in his approach and attitude toward his patients and their confidence in him. He was a great admirer of Caleb Hillier Parry (1775 1822), "the distinguished old Bath physician" as he called him, and one wonders whether he had noted a dictum of Parry: "It is much more important to know what sort of a patient has a disease, than what sort of disease a patient has."

The medical internes usually spent some time working in one of the Dispensary clinics. I worked in the Neurological Clinic under Dr. Harry Thomas, an amiable Baltimore Quaker and a competent and well-trained neurologist. I received good training in the common neurological ailments.

The most striking patient that I recall was a teen-age girl with progressive lipodystrophy.

Dr. Osler seldom missed a chance to follow to the autopsy room any of his patients who succumbed, thus following in the footsteps of the Guy's Hospital group—Bright, Addison, and Hodgkin. When an autopsy was held, it was the duty of one of his internes to record the notes dictated by the pathologist. This job often fell to me and was of great value not only because the findings were frequently interesting and instructive, but also because in this way I learned the autopsy routine. Most of the autopsies were done by Dr. Simon Flexner since Dr. Welch, with his multifarious activities, was not always in the laboratory. When I later became a member of Dr. Welch's staff, this training stood me in good stead.

I ended my year with Dr. Osler on May 1, 1895 with a feeling of deep satisfaction that I had been given an opportunity to work with the master clinician of that day. He was not only a great doctor but a great humanist with a wide knowledge of good literature and was himself a distinguished contributor of interesting essays, some of them nonmedical in scope.

III. PATHOLOGY AND BACTERIOLOGY

> A conflict of citizens in a cell state, brought about by external forces.
>
> Rudolf Virchow

When my year with "the Chief" was up, Dr. Welch, "Popsy" to the boys although he was a bachelor, asked me to join his staff as Assistant in Pathology at a small salary but with residence in the Johns Hopkins Hospital which included board and laundry. I accepted his offer with alacrity for I had already tasted his quality in the course in pathology and bacteriology which I had taken in 1893 and I had not forgotten Dr. Murray's advice to jump at a chance to work with Dr. Welch if it ever came my way.

William Henry Welch came of an old Litchfield County, Connecticut family, many members of which went into medicine. He was of medium height, inclined to plumpness, was kindly and thoughtful, especially where his staff was concerned, and had an extraordinary mind, perhaps best described as encyclopedic. In the hospital medical meetings he would get up to discuss a paper, often remarking that some well known physician had written an interesting article on the subject and citing not only his name but the year and even the page of the journal in which the article appeared. After the meetings, which were held in the Hospital library, we sometimes checked up his citations and seldom found him to be incorrect. Dr. Howard Kelly had given the hospital a number of engravings of celebrated physi-

cians which hung in the resident's parlor and I shall never forget Dr. Welch giving an entirely impromptu talk on these pictures to the residents which clearly showed that he was widely read in medical history.

While Dr. Osler was a "lark," Dr. Welch was an "owl." He lived in lodgings on Charles Street and his working room was lined with books, while most of the chairs were piled high with medical magazines. He would work until 2 or 3 o'clock in the morning, sleep fairly late, and then go over to the Maryland Club, only a block or two away, for breakfast. He always wrote his letters in longhand and never acquired the habit of dictating them to a secretary. He was greatly interested in public health and other activities outside of his regular work. He was for years a member of the Maryland Board of Health and was instrumental in helping to organize the Rockefeller Foundation for Medical Research, of which he was a trustee. He often made trips out into the country around Baltimore to make postmortems on cases of any disease in which he was especially interested. At one time he was studying hog cholera and was informed of some deaths among the swine on a farm near Baltimore and went down with his autopsy kit to examine them. It was summer, decidedly hot, and the dead animals were a trifle over-ripe. However, with the help of a colored farmhand, he autopsied one or two of the animals—an unpleasant job as they were definitely putrified. He received no remuneration for this kind of work but this his colored helper did not know. After Dr. Welch had gone, the colored man is reported to have said to his employer: "My Gawd Massa George, what some folks will do fo money."

Because of his many outside activities there were times when Dr. Welch did not appear at the laboratory for several days, but when he was there he was always ready to call his younger assistants into his room and show them any unusual specimens. To me the most memorable occasion was the time he showed me sections from a lesion from the thigh of Grover Cleveland, then President of the United States. Dr. Welch explained to me confidentially that several years before, President Cleveland had been secretly operated on for a malignant growth of the jaw and that the question was whether the mass from the thigh was a late metastasis from that growth. After much study he decided that the section of tissue was not a sarcoma but merely granulation tissue. He reached this conclusion mainly because he noticed that the blood vessels ran parallel to one another and at right angles to the surface. Years later the story of the original operation came out in the *Saturday Evening Post*.

One of my duties was to select from the museum and to prepare sections of the material used in teaching the pathology course for the second-year

students of the Johns Hopkins Medical School. One day I cut some sections of tissue from a jar labeled "epithelioma of the skin." When I had studied them, for they had to be submitted to Dr. Welch or to Dr. Simon Flexner before they were chosen for the class, I found a most extraordinary picture which I was unable to interpret. I took it to Dr. Welch who, scanning it under his microscope, said "That is a section of sponge." He explained that before the days of skin grafting a patient from whom a surgeon had removed an extensive skin growth might be left with a large disfiguring wound. In order to facilitate healing the surgeon would graft a thin slice of ordinary sponge to fill in the gap. This acted as a scaffolding for the regenerating tissue cells and made healing more rapid with less deformity. In this particular patient the cancer had recurred and on its removal not only the growth but the sponge graft had been extirpated.

Some of Dr. Welch's friends in New York, notably Dr. Gill Wylie, still sent him material removed at operation for diagnosis and, in addition, odd specimens were sent to him from various parts of the country. It usually fell to my lot to prepare, section, and stain this material and to leave it in Dr. Welch's room for examination. There were two cleaners in the laboratory, Schutz and Joe (whose last name I have forgotten), but neither of them had been trained to cut sections. However, Dr. Welch finally employed a medical student named Cox who took a lot of this work off our hands.

The staff during my term of service consisted of Dr. Flexner, an efficient, kindly, and helpful chief who, as I have said, took Dr. Welch's place when he was absent, Dr. Louis Livingood, the Fellow in Pathology, an able and likeable colleague, and myself—a harmonious group. Louis Livingood lost his life a few years later in the sinking of the French liner *Bourgogne*. In addition to demonstrating pathology and bacteriology to the second-year Hopkins medical students, we did the same in surgical pathology to the senior students. On one occasion I gave the course in bacteriology to the graduate students, for the graduate course for doctors which I had taken in 1893 was still given in 1896.

Dr. Welch or Dr. Flexner did most of the autopsies, but I did some of them. Notes were always dictated as an autopsy was in progress and cultures were taken routinely from the heart's blood and the main organs in every case. If there were local inflammatory lesions, these also were cultured. Frozen sections were made and studied from organs like the heart, liver, and kidney which might show fatty change or some lesion less noticeable in hardened than in fresh sections. Pieces of all the organs and of diseased tissue were hardened and later sectioned and stained, usually by

Mr. Cox or the man who did the autopsy, and a description of the findings was added to the record. The tissues were often hardened in alcohol, but Muller's fluid was also used and, towards the end of my term of service, Orth's fluid, which was Muller's fluid plus formalin. Celloidin was commonly used for embedding, though paraffin was used where there was an indication for serial sections. The routine stain was hematoxylin and eosin, but occasionally Van Gieson's connective tissue stain was employed or, in the case of tissue from the brain or cord, some special nerve stain. If cultures from an autopsy were positive, the one doing the work had to grow them on different media and identify the organism. A note of the findings was added to the record.

There were also some odd jobs. Dr. Welch was still studying cases of infection with the gas bacillus which he and Dr. Nuttall had described. The organism was then called *Bacillus Aerogenes Capsulatus*, and when a suspicious case turned up, blood or tissue fluid was inoculated into the ear vein of a rabbit which was then killed and placed in the ice box and later studied. Dr. Flexner was working at that time on the poisonous substances obtained from the castor oil bean, ricin and abrin. On the top floor of the laboratory, then occupied by the Department of Pharmacology, "Bunny" Aldrich was working on the secretion of the anal glands of the skunk. At times this was very obvious even on the floor below, and it was stated on good authority that when "Bunny" boarded the streetcar for home, he occupied the rearmost seat and most of the other passengers moved as far forward as possible.

At that time there were few laboratories in the United States training men in pathology and bacteriology and, as a consequence, Dr. Welch was often called on for young men available to fill positions as teachers in those subjects, this being a period when the appointment of full-time instructors in the preclinical subjects was developing rapidly. On one occasion "Popsy" sent for me and asked whether I would like to go to Australia. I declined, though one branch of my family had migrated to Australia in the middle of the nineteenth century and I had many cousins in New South Wales, several of whom were physicians. In the summer of 1896 Dr. Welch again sent for me and asked if I would consider going to Albany, New York, as Director of the Bender Hygienic Laboratory, then nearing completion. The institution was connected with the Albany Medical College, technically the medical department of Union College in Schenectady, and the director was to be responsible for the teaching of histology, pathology and bacteriology to the students of the Albany Medical College. After due consideration I accepted the position and in the fall of 1896 went to Albany and found

suitable lodgings about a mile from the laboratory which was finished except for the working benches in the large teaching room on the second floor. These took a week or two to complete, and instruction, which consisted of a preliminary talk in the amphitheater downstairs followed by the study of sections upstairs, began. I took with me as my assistant, August Jerome Lartigau, a talented young San Franciscan whom I had met when he was a graduate student at Hopkins. We had a janitor who kept the building and apparatus clean, and a student, Ed Hanes, who was an expert stenographer and helped pay his way through college by typing the records and correspondence.

In those days laboratories were few and far between and, as a consequence, we not only did the autopsies for the Albany Hospital, then downtown but later rebuilt near the laboratory, but also for Saint Peter's Hospital, the Child's Hospital, and the Homeopathic Hospital in Albany, for the Troy Hospital in Troy (and later for the new Samaritan Hospital there) and the Ellis Hospital in Schenectady. We also did a good many autopsies on private patients in their homes, usually on undertakers' trestles, a back-breaking process, and we did some post-mortems for Dr. Carroll the jail physician and for Dr. Andrew MacFarlane at the Albany Orphan Asylum. All of the surgical material removed at the Albany Hospital was examined and much of it was demonstrated to the students. Typewritten reports on the results of such examinations were sent to the Hospital to be filed with the histories. Dr. Grant Madill of Ogdensburg sent us the specimens from his large surgical practice, so we had no lack of material. In addition we examined diphtheria cultures and sputum for the Albany Board of Health and for a time also for the city of Pittsfield, Massachusetts.

When the city of Albany built a water filtration plant, we had a special assistant, Leonard Wachter, who had a small laboratory at the plant where he made daily bacteriological examinations of the filtered water. This came directly from the Hudson River into which the city of Troy, only five miles above Albany, emptied its sewage. As some joker remarked, "The citizens of Albany could always tell when the asparagus season started in Troy." The installation of this sand filtration plant greatly reduced the incidence of typhoid fever in Albany. Two or three years later I was appointed Director of the Bureau of Pathology and Bacteriology of the New York State Department of Health and we examined for them diphtheria cultures from small towns, drinking water suspected of contamination, and the brains of dogs who possibly were rabid. Before I left Albany, the State rented the third floor of the laboratory, and this work, along with the manufacture of

diphtheria antitoxin in a nearby stable, was turned over to Dr. Herbert D. Pease who had a full-time appointment.

Seven educationally profitable years were spent at Albany where I was at first Adjunct and later Professor of Pathology and Bacteriology in the Medical School. I made many friends among members of the faculty and practitioners in the neighboring cities. I became associated with J. Montgomery Mosher and Andrew MacFarlane in editing the *Albany Medical Annals*, the journal of the Alumni Association of the Medical School, and wrote a good many editorials, scientific reviews, and original articles for it. In 1897 I was allowed to take a summer semester at the University of Munich Medical School where I attended the autopsies of Professor Otto Bollinger, the discoverer of the Ray fungus. I also took lessons in German which I had not had in school. In those days Munich was a delightful spot with its two large art galleries, splendid music and opera, and interesting surrounding country which I explored, usually on my bicycle or occasionally by train. I went once or twice to Berchtesgaden which later became the hideaway of Adolf Hitler.

The Albany Medical College was at this time a flourishing institution beginning to emerge from the old proprietary type of medical school; it was technically affiliated with Union College. The Professor of Chemistry and Dean, Willis G. Tucker, was a good administrator and one of those individuals with an extraordinary memory for names. If an old student came back and visited him, he could always remember not only his surname but also his Christian name and his nickname. Joseph Craig, a large, distinguished-looking, white-haired man, was Professor of Anatomy and also City Health Officer. Hermon Camp Gordinier, an acute clinician from Troy and an authority on the local flora, was the efficient Professor of Physiology. He did a good deal of consultation work and it is recorded that on one occasion a teen-age boy whose father was very sick was met by a family friend who enquired about his father. "I am afraid he is very sick," said the boy, "for yesterday the family doctor asked for a consultation." "Whom did they bring in?" asked the friend. "I am not sure of his name," said the boy, "but it was something like nearer my God to thee."

Dr. Henry Hun, the Professor of Medicine, was a thoroughly competent internist, for many years secretary of the Association of American Physicians and author of an interesting book on diagnostic symptoms. He, Albert Vander Veer, the well-known Professor of Surgery, and Howard Van Rensselaer, Professor of Therapeutics, were all descendants of old New York Dutch stock. James P. (Pregnancy to the students) Boyd was Professor of Obstetrics, and the specialties were covered by Cyrus Merrill

in ophthalmology, "Skinny" Curtis in dermatology, and Arthur Root in otolaryngology. A few years later pediatrics was established under Henry L. K. Shaw, and psychiatry was taught by my cousin, Dr. G. Alder Blumer, Superintendent of the Utica State Hospital, until the new Albany Hospital, which included a psychiatric ward, was built; J. Montgomery Mosher, a well-trained psychiatrist, then took over this work. Andrew MacFarlane taught physical diagnosis, and Samuel B. Ward and Willis MacDonald (fat Mac) were associates in medicine and surgery, respectively. When I went to Albany I soon learned that there was a certain amount of politics played by the Medical School faculty, and I attempted to keep out of it—with some success. As my friend Dr. Charles Culver once remarked, "The inhabitants of Albany introduce politics even into their prayers."

During my service Dr. Lartigau left to join the staff of T. Mitchell Prudden, Professor of Pathology at Columbia University's College of Physicians and Surgeons. He was succeeded by Arthur Wells Elting, a Hopkins graduate who after a year went into surgery in Albany and eventually achieved a national reputation. Arthur Turner Laird, a pupil of A. C. Abbott, the well known bacteriologist of the University of Pennsylvania, was my next assistant and stayed until 1903 when I decided to return to California on account of illness in the family. The Albany years not only gave me a thorough grounding in pathology and bacteriology but were the source of many enduring friendships with members of the faculty and other physicians in the locality and also with many old students. It was, all in all, a very satisfactory period.

IV. INTERNAL MEDICINE AND TEACHING

> The art of medicine and the science of medicine are not antagonistic but supplementary to each other.
>
> Francis Peabody

In 1903 I rented a small suite of offices on Sutter Street, San Francisco, with a classmate Joe Simpson. We had a common waiting room between our private offices. I had planned to go into general practice, but I soon found that patients were being referred to me by other doctors and I gradually developed a consultation practice in internal medicine. Soon after my arrival I was appointed Associate Professor of Pathology in Cooper Medical College under William Ophuls and my job was to oversee the work in clinical microscopy of students who had patients in the medical wards at the City and County Hospital. My old chief Joseph O. Hirschfelder was doing experimental work on tuberculosis and I autopsied a good

many guinea pigs for him. After a year of this work, desiring more clinical experience, I transferred to the University of California Medical School as an instructor under Dr. William Watt Kerr, an Edinburgh graduate, a busy practitioner, and a good clinician. Here I was again associated with my old friend August J. Hartigan. We helped care for patients in Dr. Kerr's ward. In addition we did autopsies on patients who died in the ward for the Professor of Pathology, Alonzo E. Taylor. His laboratory was miles away at Parnassus Heights and, automobile transportation being yet in its infancy, he would have lost a great deal of time if he had attempted to do this himself. We thus had the great advantage of checking our clinical diagnoses with the pathological findings.

In addition to being a member of the County and State Medical Societies and the American Medical Association, I belonged to an interhospital group which met at different hospitals and discussed interesting cases. Among the members were Herbert Moffitt, one of the leading internists of the day, Charles Minor Cooper, an X-ray specialist, Wallace Terry, the well-known surgeon, Howard Morrow, a competent dermatologist, and others whom I remember less well. During this period George Simmons was editor of the *Journal of the American Medical Association* and for a year or two I furnished him with a weekly editorial.

In 1905 my old chief William H. Welch became President of the American Medical Association and asked me to deliver the oration in state medicine. The Association met in Portland, Oregon, which had so few public halls that most of the sections met in churches. I gave my oration, "On the influence which the Acquisition of Tropical Territory has had on American Medicine," from a pulpit, the church making a very acceptable meeting place.

The evening of April 17, 1906 was for me a memorable one. In the last mail I received a letter from Herbert E. Smith, Dean of the Yale Medical School, asking me if I would consider occupying the chair of medicine in that institution. About 5:15 a.m. the next morning I was awakened by a small picture, which hung over the head of my bed, falling on me. I realized that an earthquake was in progress and got into the doorway—so as to have protection if the chimney came through the roof. However, the shock did not last long and after breakfast I walked downtown to my office which was undamaged and stuck some money which I had in my desk into my pocket. I then started to walk to the Main Emergency Hospital in the City Hall which, when I reached it, I found to be so badly damaged that its equipment had been transferred to the Mechanics Pavilion, a large frame building about a block or two distant. I reported to the Chief Surgeon Dr.

Hassler and asked if I could help. There were a couple of hundred patients on mattresses on the floor, many with fractured skulls from falling bricks, and Dr. Hassler asked me to look them over and decide which ones were urgently in need of hospitalization so that they could be transferred to the Army Hospital at the Presidio. A few minutes later some one yelled out, "The roof is on fire." A policeman somehow got up and put it out, but in ten or fifteen minutes fire broke out again in a new spot. Dr. Hassler ordered evacuation of the patients which was accomplished by calling in volunteers from the street and commandeering passing automobiles. All the living were evacuated before the fire got too hot but about twenty or thirty dead in one corner of the building were cremated. That night I wrote Dean Smith that I would leave for New Haven to look over the situation as soon as the acute emergency was over. For ten days I worked at the Harbor Emergency Hospital and by that time everything had quieted down and I entrained for New Haven. After meeting some of the faculty and looking over the ground I accepted the Professorship of Medicine in the Yale Medical School.

I returned to California to settle my affairs and got back to New Haven a couple of weeks before the beginning of the school year. The Yale Medical School then consisted of two buildings on York Street, an old one near the street containing the main lecture room, the Dean's office, and the Faculty Room on the first floor and laboratory space on the second floor, and a much newer, factory-type structure behind this which was entirely occupied by laboratories. Only three or four blocks to the south was the New Haven Hospital and, on a corner opposite the hospital grounds, an almost new Dispensary building erected through the generosity of Mrs. Thomas Bennett. This housed the different out-patient departments, which were arranged about a central waiting room, and contained on the upper floor rooms for senior students awaiting calls for obstetrical patients.

At that time I was responsible for a course in clinical microscopy given to second-year students, didactic lectures on internal medicine to the third-year students, and ward rounds and a weekly clinic for the senior class. In his letter inviting me to accept the professorship, Dean Smith had stated that I would be expected to eke out my salary by private practice. I rented a house with office room near the Medical School but soon found that even with an appointment system my private work was consuming too much time. After my first year, therefore, I confined my private practice to strict consultation work and never saw patients except for or with other practitioners. Meanwhile, Mrs. John Slade Ely, the widow of my predecessor,

had endowed the professorship and I became John Slade Ely Professor of Medicine.

In 1900 the Yale Medical School, founded in 1813, was in a period of transition. The school was almost lacking in endowment and received only a small contribution from the University, largely because President Hadley, influenced by advice from New York alumni and by differences of opinion with Dean Herbert E. Smith, was somewhat dubious as to the feasibility of creating a first-class medical school in a city the size of New Haven. The New Haven Hospital, which was founded by the professors of the Medical School who for several years donated a portion of their salaries to the project, had, through the manipulations of Dr. Francis Bacon, a scholarly surgeon, passed out of the control of the medical faculty whose members had only partial use of the ward patients, though the attending physicians not connected with the institution generously allowed the clinical teachers to use their ward patients for teaching purposes. However, this was not the same as having complete control.

This situation was considerably ameliorated as a result of the report of Abraham Flexner to the Carnegie Foundation in 1910 and the annual reports of the Council on Medical Education of the American Medical Association. Mr. Flexner commented favorably on the Yale Medical School, and his report and those of the Council on Medical Education led to the discontinuance of a good many weak schools or occasionally to consolidations which resulted in improvement. Apparently this has the effect of encouraging donors to give endowments for buildings and professorships. At Yale the magnificent gift of Mr. Sterling whose trustees permitted income for either buildings or endowed professorships was ultimately of immeasurable value to the Medical School. Mr. Anthony N. Brady of Albany, New York, set the ball a rolling by donating a fund for the construction of a new pathological laboratory, financial assistance was obtained from foundations, largely through the efforts of the Reverend Anson Phelps Stokes, Secretary to the University, and a new private ward and an isolation ward were built on the hospital grounds.

A year or two before the United States entered World War I Mrs. William Wirt Winchester of San Jose, California, the widow of a former New Haven member of the well-known Winchester family, gave a large sum for the construction and endowment of a hospital for tuberculosis. Land was purchased in West Haven, about three miles from the main hospital, and the William Wirt Winchester hospital, completed just as we entered World War I, was leased to the government until the war ended. During this period the original charter of the New Haven Hospital, which

forbade doctors to charge fees even to private patients, was amended so as to permit them to charge private and semiprivate patients but not ward patients. After several meetings of the Board of Directors of the Hospital with the Faculty of the Medical School, representatives of the University, and with the attending physicians not on the teaching staff, the last named generously gave up their ward rights, but retained the right to treat pay patients in the private and semiprivate rooms. These events occurred during my term as Dean between 1910 and 1920. In 1918 further endowment was obtained when the Medical Faculty agreed to go on the full time plan. I personally agreed to try the plan for a year but at the end of that time decided that I could not be happy under it and was transferred to a clinical professorship which I retained until my active teaching career was terminated under the age limits set by the University.

I was succeeded as Dean in 1920 by Milton C. Winternitz, the Professor of Pathology and an able and dynamic pupil of my old chief William H. Welch. During his term Dr. Winternitz substantially increased the endowment and was able to obtain funds from the Sterling Foundation to build the new medical school building, the Sterling Hall of Medicine, and the communicating Institute of Human Relations on land opposite the hospital on the Cedar Street side. In the Institute were quarters for the study of human relations, Arnold Gesell's productive department for the study of child behavior, and some 20 beds for the investigation of acute psychoses and psychoneuroses under a competent staff of psychologists and psychiatrists headed by Eugen Kahn. These psychiatrists were freely available for the study of the patients in the main hospital, a very important innovation.

During the period between 1900 and my retirement in 1940 a number of changes in the Medical School took place which seem worthy of record: the entrance requirements were raised to three years of academic work including courses in inorganic and organic chemistry, biology, and physics; women students were admitted on the same basis as men; the number of students admitted to the freshman class was limited so that too many to use the available supply of clinical material would not be taken in; no student was accepted without a personal interview; didactic teaching was sharply curtailed and laboratory and bedside teaching was greatly increased; a limited system of elective courses was introduced; the hospital teaching was transferred to the third year and the dispensary work to the fourth year; the system of a graded resident staff was put into operation; the facilities for the laboratory work of the students who had patients on the wards and for the work and research of the hospital staff were greatly

increased and new departments necessitated by the increase of knowledge or by new endowments were added.

The increased endowments, including those for new chairs, and the losses of faculty members through resignation, retirement, or death naturally caused changes in the faculty of the School. The chair of surgery, vacant in 1906 by the retirement of Dr. William H. Carmalt, was filled by the appointment of Joseph Marshall Flint, an able surgeon and organizer trained by W. H. Halsted, who brought as his associate John Woodman Churchman, a competent urologist. Dr. Flint originated the idea of mobile hospitals and in World War I was in command of Mobile Hospital No. 1, manned chiefly by Yale men. He returned to civilian life after the war in poor health and retired, being succeeded by Samuel Clark Harvey, a graduate of the Yale Medical School and a pupil of Harvey Cushing.

The chair of anatomy was in the hands of Harry Burr Ferris, the most popular teacher in the School; Dr. Ferris was also an anthropologist. He had as his chief assistant Davenport Hooker and, after Hooker went to the University of Pittsburgh as Professor of Anatomy, Harold Saxton Burr who did valuable experimental work on electrical discharges from organs.

The physical side of physiology was taught by Yandell Henderson, a talented and stimulating investigator who probably initiated more theses among the graduating students than any other member of the faculty. Materia medica and therapeutics was taught by Oliver T. Osborne, a well-known authority on the subject, and physiological chemistry by Lafayette Mendel of the Sheffield Scientific School who, with the Director Russell H. Chittenden, initiated much research in this field. Obstetrics and gynecology was in the hands of Otto Gustav Ramsay, a pupil of Howard Kelly of the Hopkins, and, after his untimely death from pneumonia, by Josiah M. Slemons, another Hopkins graduate who brought with him as his assistant Arthur H. Morse. After Dr. Slemons migrated to California, Dr. Morse became head of the department with Herbert Thoms as his associate.

The specialties were covered by Arthur N. Alling, an able ophthalmologist, Henry Swan and Frederick N. Sperry, excellent otolaryngologists, and Ralph McDonnell, one of the early users of the X-rays in dermatology who finally died, as did so many of the early radiologists, as the result of a neoplasm.

As the endowment of the School increased new men were added: in internal medicine, Frances G. Blake, a well-trained internist with a flair for research, headed the department and had as his associate John P. Peters, an expert in diseases of metabolism. Harold Marvin, a cardiologist, James Fox, a neurologist, and John Paul, a student of infectious diseases. Dr.

Churchman resigned after World War I and his place was taken by Dr. Clyde Deming. A neurosurgeon William J. German, and Ashley Oughterson, a surgeon interested in peripheral vascular disease, were added to the staff. A pediatric staff headed by Edwards Park and Grover Powers was developed with James Trask and Daniel C. Darrow in charge of infectious and chemical problems respectively. James A. Honeij became the head of the X-ray Department. Many able men not on full time continued to be associated with the school as part-time teachers: Wilder Tileston and Charles Comfort in medicine, William F. Verdi in surgery, Alfred Nadler in dermatology, Max Mailhouse in neurology, and others. The end result was a well-organized school with a growing and merited reputation.

After my retirement in 1940 we moved to San Marino, California, a suburb of Pasadena, returning to Connecticut for the summer every other year. In 1942, during World War II, I taught again in the Yale Medical School during the summer to help out the depleted staff. In Pasadena I became associated with the Huntington Memorial Hospital, meeting the internes once a week at lunch and then examining and discussing interesting patients for an hour or two. I also lectured to the nurses. At the Pasadena Dispensary adjacent to the Hospital I found that the heart clinic had been abandoned because the attending physicians were in service and I took it over with the help of Dr. Donald Edmeades and later Dr. George Griffith also. For several years I prepared the clinical histories for the Clinical-Pathological Conference for Dr. Alvin G. Foord, the Pathologist to the Hospital in charge of this work. I continued until 1947 when a coronary attack ended my active career. As I once said to an old doctor whom I saw in the early morning hours with a myocardial infarction "Well Sir, I am afraid you have the favorite doctor's disease." "Yes," said he, "but not the doctor's favorite disease." So ended 55 years of active work.

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EXPERIMENTAL CEREBRAL MUCORMYCOSIS IN RABBITS WITH ALLOXAN DIABETES§

Cerebral mucormycosis in man is an unusual, generally fatal, fungus infection, occurring chiefly in patients with diabetic acidosis. Clinically, the infection is characterized by unilateral ophthalmoplegia and meningoencephalitis. At autopsy the orbital tissues, meninges, and brain are invaded by fungus. Involvement of the paranasal sinuses has been noted in a few instances. In the past the fungus had not been isolated by culture and was classified as *Mucor* on the basis of its morphology in histologic preparations. The phycomycete *Rhizopus oryzae* of the order *Mucorales* has recently been isolated at autopsy in this laboratory from a diabetic patient who died with this infection. The clinical aspects of this unusual disorder, the autopsy findings, mycologic studies, and a review of the literature have already been reported.[1] The lesions of cerebral mucormycosis were reproduced experimentally in diabetic rabbits infected with several species of fungi of the order *Mucorales*.

MATERIAL AND METHODS

Details concerning all data are shown in Tables 1 and 2.

Experimental diabetes was produced in male rabbits ranging from 2,000 to 3,600 gm. in weight by intravenous injection of alloxan in doses of 200 mgm. per kilogram body weight. The alloxan was dissolved in normal saline to a concentration of 20 mgm. per cc. Following the administration of alloxan, three to four injections of 15-20 cc. of 10% glucose in distilled water were given intraperitoneally at two-hour intervals to counteract hypoglycemia induced by the release of insulin. The presence of diabetes was ascertained daily throughout the experiment by the appearance of sugar and acetone in the urine and by blood sugar levels determined by the micro method of Nelson.[2] Appreciable hyperglycemia appeared within 48 to 72 hours after injection of

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alloxan at which time the animals were infected by intranasal instillation of 1.5 cc. of a suspension of fungus spores in saline. The suspension was prepared from sporangia obtained by growing the fungus in tubes of Sabouraud dextrose agar incubated at 25° C. for seven days. Sporangiospores were liberated by covering the culture with sterile physiologic saline and disrupting the sporangia by vigorously rubbing the growth with a heavy needle. The saline suspensions of spores from several tubes were pooled and freed of mycelial and sporangial fragments by filtration through a double layer of sterile gauze.

DIABETIC RABBITS INFECTED WITH RHIZOPUS ORYZAE

RABBIT NUMBER	BLOOD SUGAR	URINE SUGAR	URINE ACETONE	SURVIVAL HOURS	FUNGUS LESIONS		REMARKS
					NOSE	BRAIN	
725	—	3+ 4+	2+ Tr	168	—	—	
726	—	4+ 4+	0 4+	45	+	—	
728	490 434	4+ 4+	0 4+	30	+	—	
729	490	3+	Tr	5	—	—	
734	466 470	4+ 4+	0 4+	55	+	?	
741	416 650	4+ 4+	4+ 4+	42	+	+	BRONCHOPNEUMONIA NEPHRITIS
743	406	4+ 4+	4+ 4+	18	+	—	" "
744	406 422	4+ 4+	4+ 4+	41	+	+	
745	436 414	3+ 4+	0 2+	71	+	+	BRONCHOPNEUMONIA

TABLE I

In other experiments which yielded similar results and are to be reported later the spore suspensions were standardized to give a light transmittance of 35% on a Coleman Universal Spectrophotometer (Model 14) set at a wave length of 600 mμ.

The animals were sacrificed moribund or autopsied within two hours post-mortem at time intervals ranging from 5 to 168 hours after infection. Complete autopsies were performed and the tissues fixed in Zenker's fluid with 5% glacial acetic acid and in 10% formalin. Histologic preparations were made from all tissues and stained routinely with hematoxylin phloxine and with the Gram and the Giemsa method where lesions were present. Tissue fragments from the nose, lung, and spleen of all animals infected with *Rhizopus oryzae* were planted in thioglycollate broth and on Sabouraud-dextrose agar. Fungus cultures only were taken from the remaining three groups.

Controls consisted of normal, non-diabetic male rabbits infected with aliquots of the spore suspensions. A control was sacrificed with each diabetic animal.

The first group consisted of nine diabetic and nine normal rabbits infected with *Rhizopus oryzae*. The second group, consisting of three diabetic and three control animals, was infected with *Rhizopus arrhizus*. The third group of three diabetic and two control animals was infected with *Absidia ramosa*, and the fourth group, composed of three diabetic and three control rabbits, was inoculated with *Absidia corymbifera*.

These species of *Mucorales* had all been isolated from patients with mucormycosis and were given to us by Dr. Libero Ajello,* Chief, Mycology Section, Communicable Disease Center, Department of Health, Education and Welfare, Chamblee, Georgia.

RESULTS

Nearly all animals treated with alloxan developed a picture closely resembling diabetic acidosis and coma in man. Hyperglycemia, glycosuria,

DIABETIC RABBITS INFECTED WITH OTHER MUCORALES

RABBIT NUMBER	BLOOD SUGAR	URINE SUGAR	URINE ACETONE	SURVIVAL HOURS	FUNGUS LESIONS NOSE	FUNGUS LESIONS BRAIN	REMARKS
			RHIZOPUS ARRHIZUS				
760	465 697	4+ 4+	2+ 4+	18	+	—	BRONCHOPNEUMONIA NEPHRITIS
761	452 538	4+ 4+	4+ 2+	46	+	+	
766	438 441	4+ 4+	Tr 4+	35	+	+	
			ABSIDIA RAMOSA				
757	442 499	4+ 4+	Tr 4+	22	+	+	BRONCHOPNEUMONIA
758	661	4+ 4+	4+ 4+	10	+	—	
759	438 492	4+ 4+	Tr 4+	12	+	—	
			ABSIDIA CORYMBIFERA				
753	260 554	0 3+	0 Tr	70	—	—	
755	460 535	0 3+	0 4+	51	—	—	
756	506 608	4+ 4+	4+ 4+	20	+	+	BRONCHOPNEUMONIA

TABLE II

acetonuria, hyperlipemia, dehydration, and Kussmaul respiration were present.

The incidence and distribution of fungus lesions among the diabetic rabbits are shown in Tables 1, 2, and 3. Nasal lesions were present in seven animals of the first group (*Rhizopus oryzae*), in all three rabbits of the second (*Rhizopus arrhizus*) and third (*Absidia ramosa*) groups, and in one of the fourth (*Absidia corymbifera*) group. Meningoencephalitis occurred three times in the first, twice in the second, and once each in the third and fourth groups. Bronchopneumonia was encountered in three animals infected with *Rhizopus oryzae* and with *Absidia ramosa*, and in one rabbit among those inoculated with *Rhizopus arrhizus* and *Absidia corymbifera*. Nephritis was found twice in the first and once in the second group.

* We are indebted to Dr. Ajello for making these fungi available to us and for preparing the spore suspensions.

The results of infection in the non-diabetic control animals as compared with the diabetic rabbits are listed in Table 3 and show the occurrence of minimal nasal lesions in one animal of each group except the third.

Bacterial cultures from the nose were noncontributory, yielding a wide variety of microorganisms from both diabetic and control animals. All but two diabetic and two non-diabetic rabbits had positive fungus cultures from

INCIDENCE AND DISTRIBUTION OF LESIONS IN DIABETIC AND NON-DIABETIC RABBITS

RHIZOPUS ORYZAE	Nasal lesions	Meningo encephalitis	Broncho pneumonia	Nephritis
9 DIABETIC RABBITS	*7*	*3*	*3*	*2*
9 NORMAL RABBITS	1	0	0	0
RHIZOPUS ARRHIZUS				
3 DIABETIC RABBITS	*3*	*2*	*1*	*1*
2 NORMAL RABBITS	1	0	0	0
ABSIDIA RAMOSA				
3 DIABETIC RABBITS	*3*	*1*	*3*	*0*
3 NORMAL RABBITS	0	0	0	0
ABSIDIA CORYMBIFERA				
3 DIABETIC RABBITS	*1*	*1*	*1*	*0*
3 NORMAL RABBITS	1	0	0	0

TABLE III

the nose. Lung cultures for fungus were positive in 9 of 18 diabetic animals and in 11 of 16 controls.

In the diabetic rabbits the nasal lesions showed ulceration of the mucosa (Fig. 1) covered by purulent exudate composed of necrotic epithelium, polymorphonuclear leukocytes, which frequently showed signs of degeneration, many large branching aseptate hyphae (Fig. 2), and a wide variety of gram positive and gram negative bacteria. The adjacent tissues displayed coagulation necrosis with a mild peripheral infiltration of polymorphonuclear leukocytes. The necrosis and its attendant inflammation extended beyond the soft tissues and produced osteomyelitis of the nasal bones and the base of the anterior cranial fossa (Fig. 3). Many hyphae were seen singly or in aggregates throughout the involved tissues. Individual mycelia were present in capillaries. Fungus commonly invaded the walls and

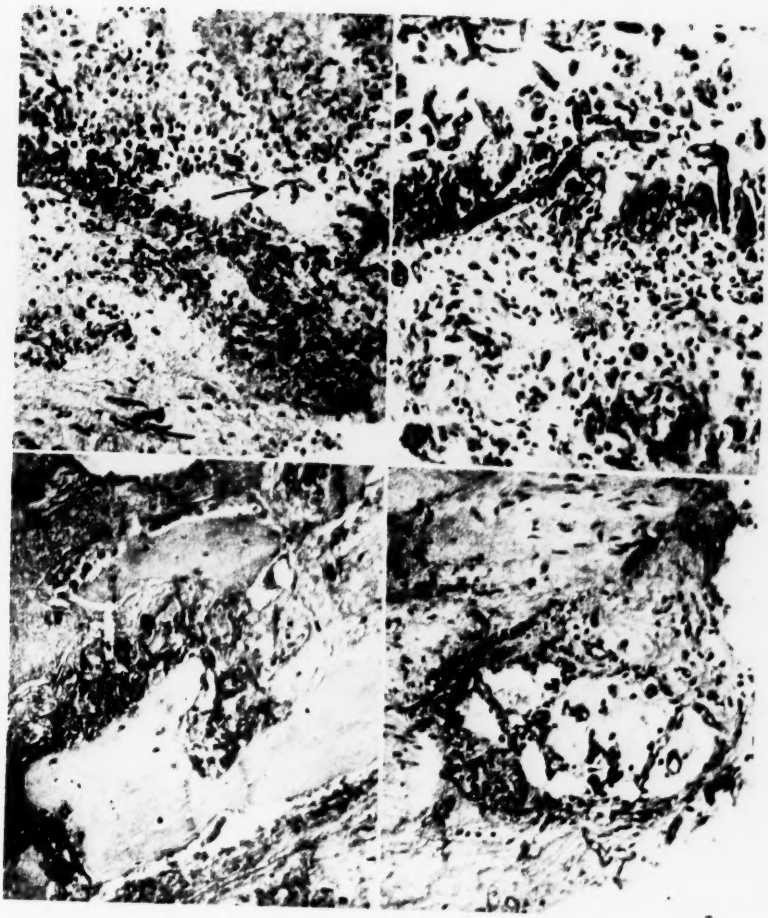

FIG. 1. Diabetic rabbit. Nasal mucosa with ulceration and acute inflammation. Several hyphae (arrows) are visible among the exudate and in the tissue. Gomori ×500.

FIG. 2. Diabetic rabbit. Inflamed nasal mucosa with many large aseptate branching hyphae of *Rhizopus* sp. Gomori ×500.

FIG. 3. Diabetic rabbit. Necrotic bone with many hyphae (center). Gomori ×500.

FIG. 4. Diabetic rabbit. A vessel in nasal mucosa with hyphae in wall and lumen. Gomori ×521.

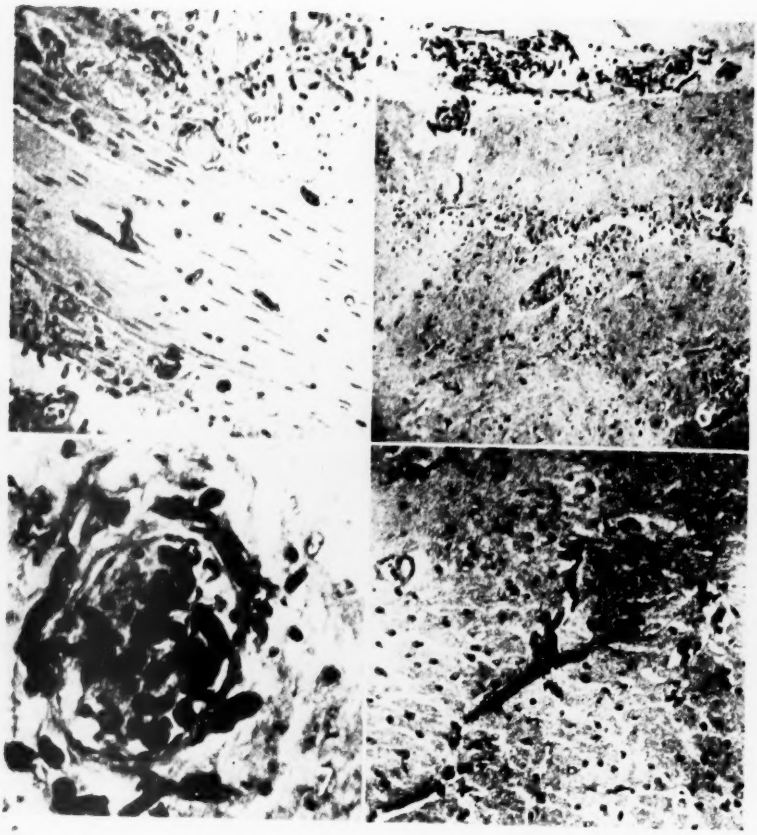

FIG. 5. Diabetic rabbit. Branch of olfactory nerve in nasal mucosa. Several mycelia, one branching, in nerve trunk and surrounding tissues. Giemsa, ×220.

FIG. 6. Diabetic rabbit. Infiltration of leptomeninges and cerebral cortex by many hyphae. Note the affinity of the fungus for the blood vessels and the necrosis of the cortex. Giemsa, ×80.

FIG. 7. Diabetic rabbit. Vessel of infarcted cerebral cortex. Hyphae occlude the lumen and invade the wall. Giemsa, ×470.

FIG. 8. Diabetic rabbit. Several hyphae without cellular injury or response in perivascular space of cerebral cortex. Giemsa, ×215.

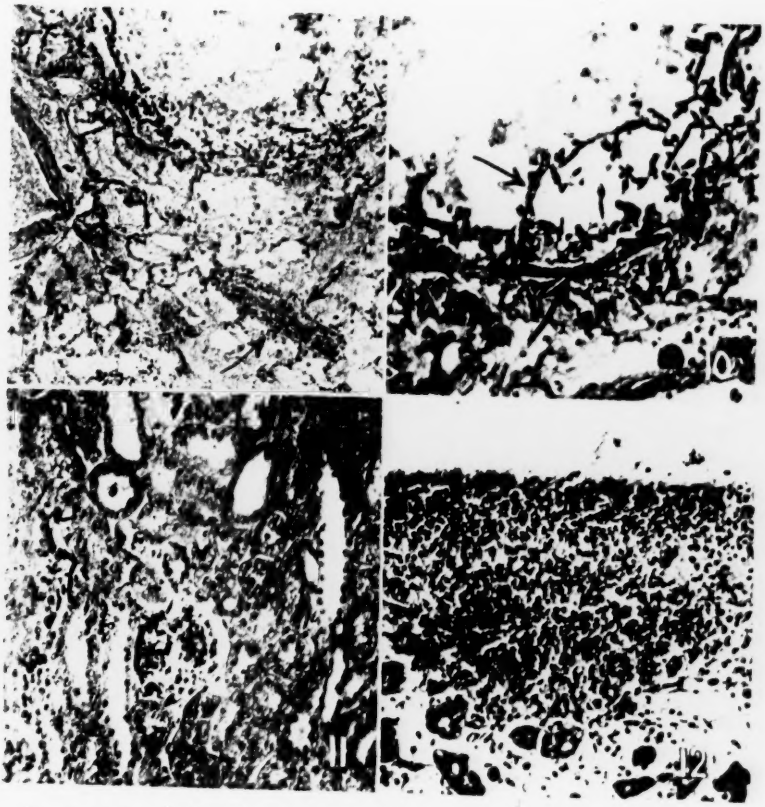

FIG. 9. Diabetic rabbit. Infarcted lung with little inflammatory reaction but many hyphae in parenchyma and bronchus. Note thrombus containing hyphae in pulmonary vein branch (arrows). Gomori. ×90.

FIG. 10. Diabetic rabbit. Bronchus invaded by hyphae. A branch of a mycelium (arrows) in the bronchial wall penetrates into the bronchial lumen. Gomori. ×90.

FIG. 11. Diabetic rabbit. Hyphae in an infarcted glomerulus and in several peritubular capillaries. Gomori. ×220.

FIG. 12. Non-diabetic rabbit. An entire lesion in the nasal mucosa is shown. Note the marked leukocyte reaction. Hematoxylin-phloxine. ×90.

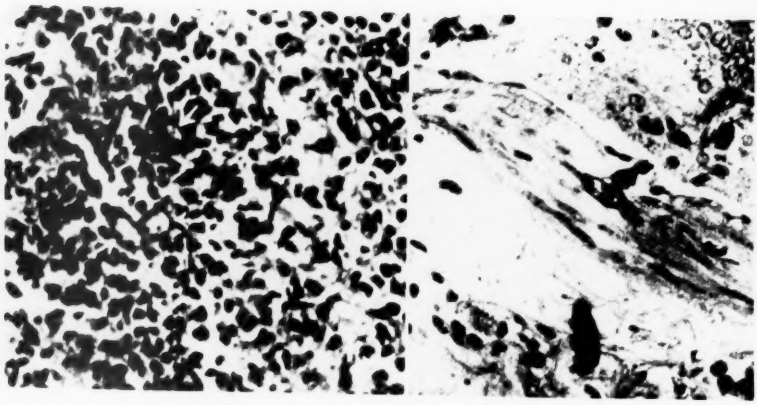

FIG. 13. Non-diabetic rabbit. The center of the lesion shown in Figure 12 contains a lipid space (arrow). Hematoxylin-phloxine. ×480.

FIG. 14. Diabetic rabbit. A branching mycelium in media of pulmonary artery branch in the process of penetrating the intima. Gomori's. ×200.

lumens of blood vessels (Fig. 4) and occasionally a mycelium was seen in the media penetrating the intima and to extend into the lumen. Similar but less extensive growth of hyphae was found in branches of the olfactory nerve (Fig. 5). The invasion of blood vessel walls and nerve trunks was often unattended by any cellular response.

The cerebral lesions involved the inferior aspects of the frontal lobes and the optic and olfactory nerves. The leptomeninges and cerebral cortex were invaded by many mycelia (Fig. 6). A slight infiltration by polymorphonuclear leukocytes, many of which appeared to be degenerating, was present in the leptomeninges and to a lesser extent in the cortex. The latter showed early necrosis which appeared to result from extensive involvement of the blood vessels by fungus. Mycelial masses intermingled with strands of fibrin and polymorphonuclear leukocytes occluded the vascular lumens, and the vessel walls were also heavily invaded by hyphae (Fig. 7). Isolated mycelia without signs of associated cellular injury or response were frequently present in the perivascular spaces of the brain (Fig. 8).

The lungs showed foci of bronchopneumonia and infarction. The smaller lesions were fairly well circumscribed and consisted of a few hyphae surrounded by moderate numbers of polymorphonuclear leukocytes many of which showed pyknosis of the nuclei and karyorrhexis. A few large mononuclear cells were also present. The larger lesions which sometimes involved the pleura were ill-defined areas of necrosis with many mycelia (Fig. 9). Scattered polymorphonuclear leukocytes, again showing signs of degeneration, were present throughout the lesion without forming a line of demarcation. Blood vessel invasion and occlusion by the fungus were prominent and involved branches of the pulmonary artery and veins. Throughout the parenchyma occasional septal capillaries contained isolated hyphae unattended by cellular response. Extensive growth of the fungus was found in many bronchi where it involved the walls and lumens. In several instances mycelial branches penetrated through the bronchial wall and mucosa into the lumen (Fig. 10). No definite bacteria were identified in the lesions.

The renal lesions consisted of multiple foci of necrosis. These were located chiefly in the cortex and at the cortico-medullary junction and only rarely involved the medulla. The lesions were clearly the result of capillary obstruction by hyphae producing areas of infarction in which the fungus proliferated (Fig. 11). Various stages of the process were seen in the glomeruli in which one or several capillaries were occluded by mycelia with necrosis of the remaining loops. Some hyphae were encountered free in the capsular space. Mycelia were also found in the peritubular capillaries, either without evidence of cellular injury and response, or producing small in-

infarcts with disruption of the adjacent tubules. Extension of mycelia from these foci into tubules was noted. An occasional mycelium was found free in the lumen of an interlobular artery. The lesions showed no appreciable hemorrhage and only slight leukocytic response. Degenerative changes were seen in most of the polymorphonuclear leukocytes.

Lesions in the non diabetic control animals were confined to the nasal mucosa and consisted of a few, minute, circumscribed foci of ulceration surrounded by a marked infiltration with normal appearing polymorphonuclear leukocytes (Fig. 12). The lesions did not involve the tissues beyond the submucosa. Rare spores, often degenerating in appearance, were present in the center (Fig. 13). There was no involvement of blood vessels.

DISCUSSION

The lesions produced experimentally by the intranasal instillation of spore suspensions of fungi of the order *Mucorales* in rabbits with alloxan-induced diabetes closely resemble those of cerebral mucormycosis in man. The infection was readily established by this method. As already suggested by observations in patients, the nose and paranasal sinuses can be the portal of entry. Our findings show that when the infection is established in the nasal mucosa, it rapidly extends to the adjacent tissues, including the bone, and finally spreads to the leptomeninges of the frontal lobes of the brain. Invasion of the optic and olfactory nerves is another pathway by which the process reaches the brain. Invasion of blood vessel walls, associated sometimes with thrombosis, seems to account for many of the morphologic and clinical manifestations and for the dissemination of this infection. Much of the necrosis at the primary site of infection in the nasal mucosa appears related to vascular occlusion. The renal lesions clearly result from hyphae trapped in small vessels, producing infarcts in which the fungus proliferates. The origin of these mycelial emboli from pulmonary lesions in which the fungus has invaded the pulmonary veins was readily demonstrable. The fungus probably reaches the lungs by aspiration, although hematogenous lesions produced by emboli from infected veins of the nasal regions or skull are quite likely. Vascular obstruction secondary to fungus invasion of branches of the pulmonary artery plays a definite part in the progression of pulmonary lesions. Infarction resulting from involvement of the leptomeningeal vessels accounts for the changes in the cerebral cortex. These are enhanced by the proliferation of the fungus in the infarcted areas with further invasion and occlusion of cortical vessels. Mycelial emboli to distant parts of the brain have not been observed in the experimental animals although they are known to occur in patients when the intracranial portion

of the internal carotid artery is involved. All lesions of the diabetic rabbits were incompletely demarcated by a mild inflammatory reaction. This consisted almost entirely of polymorphonuclear leukocytes most of which showed pyknosis of nuclei and karyorrhexis.

The affinity of the fungus for arteries and veins is striking in both human and experimental infection but the reason remains obscure. The direct effects of the fungus on cells and tissues other than those related to vascular obstruction are as yet undetermined. The mycelia are often seen growing in tissues which show no signs of injury or cellular response. Actual penetration of apparently intact vessels (Fig. 14) or bronchial walls is frequently observed.

Among the nine diabetic rabbits inoculated with *Rhizopus oryzae* two failed to show lesions. One of these died five hours after inoculation, probably too early to develop lesions. The other, one of the first animals in the study, was sacrificed 168 hours after inoculation. In this animal marked acetonuria was not sustained. We have no explanation for the absence of lesions in two of the three animals infected with *Absidia corymbifera*.

The changes in the non-diabetic rabbits differed greatly from those of the diabetic animals. The lesions were few in number and of minute size surrounded by many polymorphonuclear leukocytes which showed no unusual degree of degenerative changes. Rare spores but no hyphae were present in these lesions. There was no spread to bone or brain and no pulmonary or renal involvement.

Rhizopus oryzae and the other *Mucorales* used in this study are ubiquitous saphrophytes which under certain unknown circumstances acquire the ability to invade tissues and spread through the body. The presence of bacteria in the nasal lesions of man and experimental animals suggests the possibility that these microorganisms may play a part in establishing the primary focus of infection. The absence of bacteria in the cerebral and renal lesions indicates, however, that these organisms are not necessary for the systemic dissemination of the fungus. From our experimental findings and observations in patients it is obvious that the metabolic alterations of diabetes mellitus are of signal importance in the pathogenesis of this infection. Mucormycosis has, however, been encountered in systemic and localized disorders which are not associated with diabetes such as leukemia, other malignancies, severe burns, infantile diarrhea, and antibiotic therapy.[7] The distinct differences in the pathogenicity of these fungi in diabetic and normal animals offer an opportunity to study the relationship of host metabolism to infection. Studies are in progress to determine the metabolic factors

which play a part in the pathogenesis of mucormycosis by either changing the virulence of the agent or altering host resistance.

SUMMARY

Our present findings show that cerebral mucormycosis can be produced experimentally in rabbits with various fungi of the order *Mucorales* and that the paranasal sinuses can be the portal of entry. Invasion of blood vessels by the fungus accounts for much of the spread of the infection and for some but not all morphologic aspects of the lesions. The inflammatory reaction was diminished in intensity in the diabetic rabbits with most of the polymorphonuclear leukocytes showing degeneration. Metabolic alterations such as are associated with diabetes mellitus appear to be an essential factor in the pathogenesis of this disorder.*

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THE ARTERIAL PATTERN IN THE HAND

INTRODUCTION

The conventional descriptions of the arteries of the hand (Cunningham,[1] Grant,[2] Gray,[3] and Morris[4]) depict a superficial volar arch formed by anastomosis of the ulnar and superficial volar radial, or occasionally the volar radial index arteries, and a deep arch formed by the radial and deep ulnar arteries. These are the major ulnar-radial anastomoses.

From the ulnar artery arise a proper digital artery to the ulnar side of the fifth digit, and three common volar digital arteries that bifurcate to form proper volar digital arteries to adjacent sides of the fifth, fourth, third, and second digits (Fig. 1).

The radial artery passes to the dorsum of the hand and gives off a dorsal carpal branch, which anastomoses with a corresponding branch of the ulnar (and interosseous arteries), forming a dorsal carpal arch. From this arch arise the second, third, and fourth dorsal metacarpal arteries and a small dorsal digital branch to the ulnar side of the fifth finger (Fig. 2). Each of these, except the last, bifurcates to form dorsal digital arteries, which supply the adjacent sides of the last four digits. The dorsal metacarpal arteries anastomose with the deep volar arch and common volar digital arteries by superior and inferior perforating arteries. The radial artery, after the dorsal carpal branch, gives off a first dorsal metacarpal, which bifurcates into branches to the first and second digits. These branches may arise from the radial artery independently. The radial artery then passes to the palmar aspect of the hand between the heads of origin of the first dorsal interosseous muscle. It traverses the deep palm to anastomose with the deep ulnar branch of the ulnar artery, thus completing the deep arch (Fig. 1).

From the deep arch arise the princeps pollicis which bifurcates into two proper digital arteries of the first digit, the volar radial index artery supplying the radial aspect of the second digit, and three volar metacarpal

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arteries. The volar radial index and volar metacarpal arteries anastomose with the corresponding common volar digital arteries at the bifurcation of the latter.

Thus apart from the two major ulnar radial arterial anastomoses the classical descriptions indicate anastomosis between the dorsal metacarpal and common volar digital arteries, and between the volar radial index and volar metacarpals and the common volar digital arteries. A fifth and occasional anastomosis is mentioned as occurring between the volar radial index artery and superficial arch.

TABLE I. TYPES OF ANASTOMOSIS BETWEEN ULNAR AND RADIAL ARTERIES IN 226 HANDS (HANDS WITH MEDIAN ARTERIES OMITTED)

Type of anastomosis	*Number of hands*	*Percentage*
U—deep ulnar/deep arch	212	94
P—superficial volar arch/princeps pollicis	150	66
D—common volar digital/volar radial index or volar metacarpal	127	56
R—superficial volar arch/superficial volar radial	74	33
M—common volar digital/dorsal metacarpal	55	24
——no anastomosis	4	2

Excellent studies of the different parts of the arterial system of the hand have been made by Adachi[1] and by Dubreuil-Chambardel.[5] In the present work attention has been directed to the arterial system as a whole and to ulnar-radial anastomoses.

MATERIALS AND METHODS

The ulnar and radial arteries of 250 hands in embalmed cadavers were injected with either plastic or acetone to which dyes were added, and all branches were dissected and recorded, including median arteries when they were present. One-hundred sixty-three hands were from Connecticut, 74 from Indiana, and 13 from Puerto Rico. One hundred thirty-one specimens were right hands; 119 were left hands. The cadavers were predominantly males in the fifth through eighth decades at the time of death.

In 113 hands the outer diameters of all branches were measured to within 0.5 mm.; diameters were estimated in the remainder. Arbitrarily the common volar digital arteries were taken as a standard. Their mean diameter was 2.5 mm. An artery of 0.25 mm. diameter would have a cross sectional area of one-hundredth that of a common volar digital artery. Consequently branches of less than 0.5 mm. diameter have been omitted from the following report as insignificant.

OBSERVATIONS

A. *Frequency of anastomosis by type*

Five types of anastomoses occurred in the following order of frequency: *deep ulnar/deep arch; superficial arch/princeps pollicis, common volar digital/volar metacarpal; superficial arch/superficial volar radial;* and *common volar digital/dorsal metacarpal.* These anastomoses have been designated U, P, D, R, and M; their actual frequencies without regard to combinations of more than one type in the same hand are given in Table 1.

TABLE 2. COMBINATIONS OF ANASTOMOSES BETWEEN ULNAR AND RADIAL ARTERIES IN 226 HANDS, AND IN 24 HANDS WITH ADDITIONAL MEDIAN ARTERY

Number of anastomoses, ulnar and radial arteries											*Ulnar, radial, and median arteries*
None	*1*		*2*		*3*		*4*		*5*		
4	U	17	UP	24	UPD	54	UPDR	27	UPDRM	3	U 1
	P	2	UD	10	UPR	9	UPDM	6			P 1
	D	2	UR	7	UPM	18	UPRM	3			UP 2
	R	1	UM	5	UDR	11	UDRM	3			UD 4
	M	1	PD	1	UDM	7					UM 2
			DM	1	URM	7					UPD 9
					PDR	2					UPM 2
											UPDR 2
											PD 1
Totals	4		23		48		108		40	3	24
%	2%		9%		19%		43%		16%	1%	10%

Anastomosis between a dorsal radial carpal and dorsal ulnar carpal artery of significant size did not occur; very rarely did it occur directly between the superficial arch and the volar radial index artery. However, anastomosis between a branch of the princeps pollicis artery and the superficial arch, not often described classically, was very common.

Details of these five types of anastomosis are described under "Major patterns"; anastomoses occurring in hands with median arteries are discussed separately.

B. *Frequency of combination of anastomotic types*

Table 2 gives the type or combination of types of anastomosis between the radial and ulnar arteries and between the radial, ulnar, and median arteries in individual hands. Very few hands had either no anastomosis or

all five anastomoses; most had three. Allowing for the almost invariable presence of a *deep ulnar/deep arch* (U) anastomosis almost every combination that could be postulated actually occurred. However, 125 hands, or half of the sample, had anastomotic patterns in the sequence U, UP, UPD, UPDR, and UPDRM. Each of these combinations was the commonest in hands with one, two, three, four, or five types of anastomosis.

Twenty four hands, or 10 per cent of the sample, had a median artery in addition to the ulnar and radial arteries. Such hands are discussed separately below.

TABLE 3. NUMBER OF DEEP ULNAR ARTERIES AND THEIR COURSE FROM THE MAIN STEM, REGION OF BIFURCATION, OR PROPER DIGITAL BRANCH TO THE FIFTH DIGIT IN 212 HANDS WITH DEEP ULNAR/DEEP ARCH ANASTOMOSIS, RELATIVE TO THE HYPOTHENAR MUSCLES

One			*Two*		*Three*
From main stem through muscle	From region of bifurcation superficial to muscle	From proper digital superficial to muscle	From main stem and bifurcation	From main stem, and proper digital	From main stem, bifurcation and proper digital
76	56	45	11	22	2

C. *Major patterns*

The common patterns are described for hands with one, two, three, four, or five different types of anastomosis as well as details of each type of anastomosis in the entire sample.

U—deep ulnar/deep arch anastomosis only (Fig. 3).

This was the only anastomosis between ulnar and radial arteries in 17 hands, or 7 per cent of the entire sample (Table 2). However, it occurred alone or in combination in 212 hands, or 94 per cent (Table 1).

Only in 76 hands, or 36 per cent of hands with a *deep ulnar/deep arch* anastomosis, did a single deep ulnar branch arise from the main stem of the ulnar artery and accompany the deep ulnar nerve through the hypothenar muscles (Table 3). In 56 hands the branch arose from, or close to, the point of bifurcation of the ulnar artery (superficial arch) into a proper digital to the ulnar side of the fifth digit and the continuing superficial arch; and in 45 hands it arose from this proper digital close to the bifurcation. Thus, in 101 hands, or 48 per cent, the deep ulnar artery arose in the

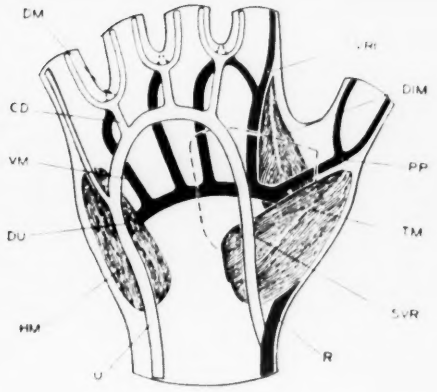

FIG. 1.

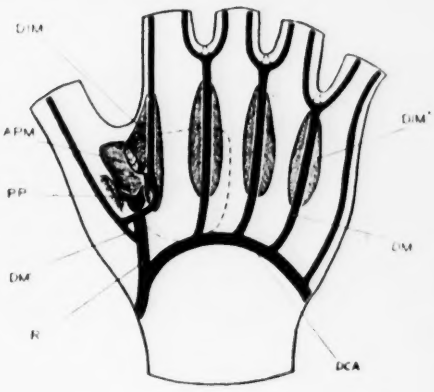

FIG. 2.

FIG. 1. Conventionally described pattern of the arteries on the volar aspect of the right hand. Key to arteries and muscles:

DM—Dorsal metacarpal artery
CD—Common volar digital artery
VM—Volar metacarpal artery
DU—Deep volar branch of ulnar artery
HM—Hypothenar muscles
U—Ulnar artery
VRI—Volar radial index artery
DIM—First dorsal interosseous muscle
PP—Princeps pollicis artery
TM—Thenar muscles
SVR—Superficial volar branch of radial artery
R—Radial artery

FIG. 2. Conventionally described pattern of the arteries on the dorsum of the right hand. A segment of the first dorsal interosseous muscle has been excised. Key to arteries and muscles:

DIM—First dorsal interosseous muscle
APM—Adductor pollicis muscle
PP—Princeps pollicis artery
DM'—First dorsal metacarpal artery
R—Radial artery
DIM'—Fourth dorsal interosseous muscles
DM—Dorsal metacarpal artery
DCA—Dorsal carpal arch

FIG. 3.

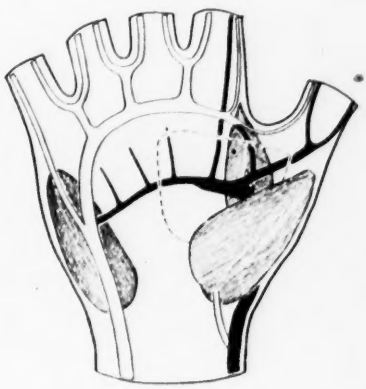

FIG. 4.

FIG. 3. Arterial branches on the volar aspect of the right hand; deep ulnar/deep volar arch anastomosis only.

FIG. 4. Arterial branches on the volar aspect of the right hand; deep ulnar/deep arch and superficial volar arch/princeps pollicis anastomoses.

region of the bifurcation and passed superficial to the hypothenar muscles to join the deep arch. Consequently, this artery has been represented thus in all except Figure 1.

In 33 hands, or 15 per cent, two deep ulnar arteries occurred, one arising from the main stem and passing through the hypothenar muscles and the other either arising from the bifurcation region or from the proper digital adjacent to it and passing superficial to the hypothenar muscles. In two hands, or 1 per cent, there were three deep ulnar arteries, one in each of the three described positions.

In the hands with only a *deep ulnar/deep arch* anastomosis, the superficial arch ended as (a) a common volar digital to the adjacent sides of the third and fourth digits (66 cases), (b) as a common volar digital to the adjacent sides of the second and third digits (66 cases—Fig. 3), or (c) extended radially to supply adjacent sides of the first and second digits (5 cases). In types (a) and (b) above, a superficial volar radial artery occasionally (4 cases) supplied the adjacent sides of the first and second digits; in all other hands this artery terminated in the thenar muscles and it never anastomosed with the superficial arch. The superficial arch did not anastomose with a branch of the princeps pollicis artery.

When the superficial volar arch only reached the adjacent sides of the third and fourth digits, the volar radial index artery was enlarged and supplied the adjacent sides of the second and third digits. No common volar digital artery anastomosed with a volar radial index, volar metacarpal, or dorsal metacarpal artery.

In 19 of the 226 hands (8 per cent) a large perforating branch from the second dorsal metacarpal artery passed volarward between the bases of the second and third metacarpal bones to make a significant contribution to the deep volar arch. In one hand this perforating artery formed the entire radial component of the deep volar arch.

UP *Deep ulnar/deep arch and superficial volar arch/princeps pollicis anastomoses; Figure 1.*

This combination occurred in 24 hands (half of those with two anastomotic types or 10 per cent of the entire sample—Table 2). However, the *superficial arch/princeps pollicis* anastomosis was found in 150 hands or 66 per cent of the 226 hands with ulnar and radial arteries only (Table 1).

The *deep ulnar/deep arch* anastomoses have been described above. The superficial arch reached radially to the interval between the first and second digits; it gave a branch, the superficial volar radial index artery, to the radial side of the second digit and a branch to the ulnar side of the first

digit (except in one hand only a superficial volar radial artery occurred). From this radialward extension the *superficial arch/princeps pollicis* anastomosis was formed with a branch from the main stem of the princeps pollicis artery (Figs. 4 and 5—14 cases), with one of the proper digital branches of the princeps pollicis artery (6 cases), or with both a branch from the main stem and a proper digital branch of the princeps pollicis artery (4 cases).

TABLE 4. SITE OF ANASTOMOSIS BETWEEN THE SUPERFICIAL ARCH AND A BRANCH OF THE PRINCEPS POLLICIS ARTERY, AND THE COURSE OF ITS SPECIAL BRANCH AND MAIN STEM ON THE DORSUM (HANDS WITH MEDIAN ARTERIES OMITTED)

Superficial arch in 150 hands anastomosing with									
proper digital branch of princeps pollicis on			special branch of princeps pollicis on		proper digital and special branch of princeps pollicis	Special branch of princeps pollicis (102 hands) passing dorsal to interosseous muscle		Main stem of princeps pollicis (226 hands) passing dorsal to interosseous muscle on	
ulnar side	radial side	both sides	ulnar side of 1st digit	radial side of 2d digit		partly	entirely	ulnar side	radial side
37	7	4	54	24	24	11	3	15	9
	32%		52%		16%	11%	3%	6%	4%

In three of the 24 hands the volar radial index artery supplied the adjacent sides of the second and third digits, and in one hand a volar metacarpal artery supplied the adjacent sides of the third and fourth digits. However, there was never any anastomosis between the volar radial index or the volar metacarpal and the corresponding common volar digital artery; the latter was absent. In one hand a superficial volar radial artery supplied both sides of the first digit (in addition to the proper digital branches of the princeps pollicis artery) but did not anastomose with the superficial arch. All other superficial volar radial arteries terminated in the thenar muscles. No dorsal metacarpal artery anastomosed with a common volar digital artery.

There were two sites for the *superficial arch/princeps pollicis* anastomosis (Table 4). In 48, or 32 per cent, of the 150 hands with this anastomosis the branch of the superficial arch to the first digit joined a proper digital branch of the princeps pollicis artery. Usually this anastomosis was on the

ulnar side of the first digit; in four hands the branch of the superficial arch bifurcated and each subdivision joined the corresponding proper digital branch of the princeps pollicis artery.

In 78, or 52 per cent, of the 150 hands a special branch of the princeps pollicis artery arose from its main stem deep to the adductor pollicis. This special branch passed over the distal border of the adductor pollicis usually to join the branch of the superficial arch to the ulnar side of the first digit (Fig. 4) but sometimes that to the radial side of the second digit (the superficial volar radial index artery). In the remaining 24 hands, or 16 per cent of the 150, anastomosis of the superficial arch occurred both with a special branch and with a proper digital branch of the princeps pollicis artery.

The princeps pollicis artery itself usually arose from the radial artery immediately after the latter had penetrated from the dorsum of the hand volarward between the two heads of origin of the first dorsal interosseous muscle (Fig. 2). However, in 14 of the 150 hands it arose immediately before this penetration. The artery then ran distally on the superficial (dorsal) aspect of the radial origin of the first dorsal interosseous muscle for approximately half (11 hands) or all (3 hands) of the width of the muscle. The princeps pollicis artery then either penetrated the dorsal interosseous (Fig. 6) or passed over its distal border to wind around the first metacarpal between the bone and the adductor pollicis to reach the volar aspect of the first digit as described classically. In such hands the special branch of the princeps pollicis artery usually continued in the superficial (dorsal) position when the main stem penetrated the dorsal interosseous and passed over the distal border of this muscle and the adductor pollicis to join the superficial arch or, if the princeps pollicis remained dorsal itself, arose as the latter passed over the distal border of the interosseous.

In 24 of the 102 hands having a special branch of the princeps pollicis artery this branch did not arise directly from the princeps pollicis artery but from the radial artery at or just proximal to its origin. Such branches passed superficial (dorsal) to the first dorsal interosseous either on its radial or ulnar origin before crossing over the distal border of the muscle. Special branches of the princeps pollicis artery with this course resemble the first dorsal metacarpal artery but, because of transitional forms between these and special branches arising from a superficial (dorsal) princeps pollicis artery (and because minute but separate first dorsal metacarpal arteries occurred in the same hands), they have been considered as analogous to other special branches of the princeps pollicis artery.

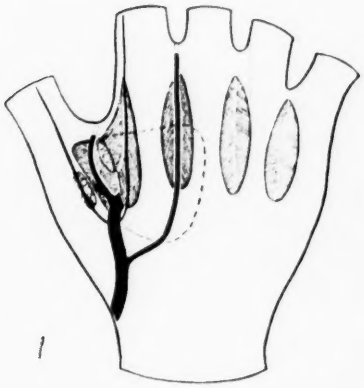

FIG. 5.

FIG. 6.

FIG. 5. Arterial pattern on the dorsum of the right hand; actual arrangement with common volar digital/dorsal metacarpal anastomosis. A special branch of the princeps pollicis artery arises deep to the first dorsal interosseous muscle and, passing distal to the adductor pollicis muscle, anastomoses with the superficial volar arch.

FIG. 6. Arterial branches on the dorsum of the right hand; actual pattern with the special branch of the princeps pollicis artery arising and passing superficially over the first dorsal interosseous muscle. The princeps pollicis also passes superficially in the initial part of its course before penetrating the radial head of the muscle.

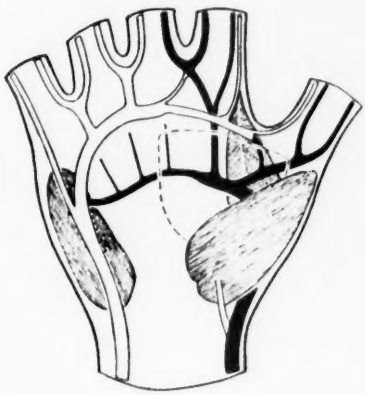

FIG. 7.

FIG. 8.

FIG. 7. Arterial branches on the volar aspect of the right hand; deep branch of ulnar/deep volar arch, superficial volar arch/princeps pollicis, and common volar digital/volar metacarpal or volar radial index anastomoses.

FIG. 8. Arterial branches on the volar aspect of the right hand; deep branch of ulnar/deep volar arch, superficial volar arch/princeps pollicis, common volar digital/volar metacarpal (volar radial index), and superficial volar arch/superficial volar branch of the radial artery.

The interval between the origins of the princeps pollicis and volar radial index arteries ranged between 0.0 cm. (common origin but no common stem) to 3.5 cm. (princeps pollicis artery arising from radial artery on the dorsum of the hand). The mean distance between the origins was 0.8 cm.; the origins might be widely separated even when both arteries arose from the radial artery after the latter had entered the volar aspect of the hand between the heads of the first dorsal interosseous muscle.

UPD; Deep ulnar/deep arch; superficial volar arch/princeps pollicis; and common volar digital/volar metacarpal anastomoses; Fig. 7.

This combination was the most frequent where three types of anastomosis were present in the same hand. It occurred in 54 hands (half of those with three anastomoses and 22 per cent of the total sample, Table 2). The *common volar digital/volar metacarpal* (or volar radial index) anastomosis occurred alone or in combination in 127 hands (56 per cent, Table 2).

The *deep ulnar/deep arch* and *superficial volar arch/princeps pollicis* anastomoses have been described above. In 47 of the 54 hands (Fig. 7) the volar radial index artery was relatively large and joined the adjacent common volar digital artery (usually at the bifurcation of the latter, but sometimes proximally, and rarely distally when it anastomosed with a proper digital). In 24 of these 47 hands one or more volar metacarpal arteries made a similar anastomosis with the corresponding common volar digital arteries in addition. In the remaining seven hands the adjacent sides of the second and third digits were usually supplied by the volar radial index artery, there being no corresponding common volar digital, and the anastomosis was formed by one or more of the more medial volar metacarpal arteries with corresponding common volar digitals. Only one hand in the 54 had a superficial volar radial artery extending beyond the thenar muscles, and this was unique in that it joined the deep arch. Thus no hand in this group had a *superficial volar arch/superficial volar radial* or a *common volar digital/dorsal metacarpal* anastomosis.

The anastomoses between common volar digital and volar metacarpal or volar radial index arteries for the 127 hands were tabulated (Table 5). The most frequent site involved the volar radial index either alone (56 per cent of hands with a *common volar digital/volar metacarpal* anastomosis) or in combination with a volar metacarpal. The second or third common volar digital was involved in only 24 per cent in each case, and the fifth finger's ulnar proper digital in only 6 per cent.

In addition to the anastomoses, 22 of the 127 hands had adjacent sides of two digits supplied by the volar radial index (8 cases; adjacent sides of the second and third digits) or the third volar metacarpal artery only (14

cases; the fourth and fifth digits, and the ulnar side of the fifth digit also in 10 cases).

In hands without a *common volar digital/volar metacarpal* anastomosis the volar radial index artery supplied the adjacent sides of the second and third digits in 10 cases and the third volar metacarpal, the ulnar side of the fifth digit in 10 cases in the absence of a corresponding common volar digital artery; and in 2 other cases adjacent sides of the third and fourth digits were supplied by the second volar metacarpal artery.

TABLE 5. SITE OF ANASTOMOSIS OF VOLAR RADIAL INDEX OR VOLAR METACARPAL WITH COMMON VOLAR DIGITAL ARTERIES IN 127 HANDS

Number of hands	*Bifurcation of common volar digital artery supplying adjacent sides of digits*			*Proper volar digital to ulnar side of 5th digit*
	2/3	3/4	4/5	
71	Anastomosis			
15	Anast.	Anast.		
7	Anast.	Anast.	Anast.	
2	Anast.	Anast.	Anast.	Anast.
5		Anast.		
2		Anast.	Anast.	
12			Anast.	
3				Anast.
8	Anast.		Anast.	
2	Anast.			Anast.
Totals 127	105	31	31	7
%	83%	24%	24%	6%

Thus, whether an anastomosis was present or not, the adjacent sides of the second and third digits received additional or sole support from the volar radial index artery in 123 hands or slightly more than half the entire sample. When anastomosis occurred for these or other adjacent digits, the main arterial supply might come from the common volar digital or the volar metacarpal (or volar radial index) artery or it might come from both equally, judging by the relative sizes of the vessels concerned.

UPDR; Deep ulnar/deep arch; superficial volar arch/princeps pollicis; common volar digital/volar metacarpal; and superficial arch/superficial volar radial anastomoses; Fig. 8.

Twenty-seven, or 67 per cent of the 40 hands with four types of anastomosis, had this combination (Table 2). A *superficial volar arch/*

superficial volar radial anastomosis occurred in 74, or 33 per cent, of the hands in the entire sample (Table 1).

The patterns of the first three anastomoses already have been described. The *superficial volar arch/superficial volar radial* anastomosis was identical in the hands with four anastomoses and in the entire sample. The superficial volar branch of the radial artery passed through or over the superficial layers of the abductor pollicis brevis and flexor pollicis brevis to anastomose with the radial end of the superficial arch (Fig. 8). (In one hand the artery, after entering the thenar muscles, penetrated the flexor retinaculum at about its mid-point to enter the palm deep to the retinaculum.) Occa-

TABLE 6. COMMON VOLAR DIGITAL/DORSAL METACARPAL ARTERY ANASTOMOSES IN 55 HANDS

Number of hands	*Dorsal metacarpal arteries concerned:*			
	1st	*2d*	*3d*	*4th*
49		Anastomosis		
3		Anast.	Anast.	
1			Anast.	Anast.
1		Anast.		Anast.
1			Anast.	
Totals 55		53	5	2

sionally the artery gave a branch, distinct from the "proper digital" branches of the superficial arch to the adjacent sides of the first and second digits, to the radial side of the first digit.

Similar superficial volar radial arteries occurred in 17 other hands, or 7 per cent of the entire sample, but did not anastomose with the superficial arch. In such cases the "proper digital" arteries to adjacent sides of the first and second digits arose from these arteries rather than from the radial end of the superficial arch. In the remaining 135 hands the superficial volar radial artery terminated in the thenar muscles.

UPDRM; Deep ulnar/deep arch; superficial volar arch/princeps pollicis; common volar digital/volar metacarpal; superficial arch/superficial volar radial; and common volar digital/dorsal metacarpal anastomoses.

Only three hands, or about one per cent of the entire sample, showed all five types of anastomosis (Table 2). In these hands, in addition to the previously described anastomoses, a *common volar digital/dorsal metacarpal* anastomosis usually was effected by the second dorsal metacarpal artery

passing distal to the heads of the second and third metacarpal bones, entering the palmar aspect of the hand, and joining the corresponding common volar digital artery at its bifurcation into proper digital arteries.

The same type of anastomosis occurred alone or in different combinations in 55 hands, or 24 per cent of the entire sample (Table 1). The anastomosing dorsal metacarpal artery was almost always the second, but occasionally the third or fourth, either alone or in combination (Table 6). The junction with the corresponding common volar digital artery was also almost always at the bifurcation but occasionally was with a proper digital artery (Fig. 5).

TABLE 7 THE INCIDENCE OF DORSAL METACARPAL ARTERIES OF SIGNIFICANT SIZE IN 156 HANDS WITH OR WITHOUT A COMMON VOLAR DIGITAL/DORSAL METACARPAL ANASTOMOSIS

Number of hands	*Dorsal metacarpal arteries (DM)*			
	1st	*2d*	*3d*	*4th*
36	DM			
42		DM		
41	DM	DM		
14	DM	DM	DM	
7	DM	DM	DM	DM
8		DM	DM	
7		DM	DM	DM
1			DM	DM
Totals 156	98	119	37	15

The dorsal carpal arch and dorsal metacarpal arteries were of insignificant size in 94 hands; the presence of one or more dorsal metacarpal arteries in the remaining 156 hands is shown in Table 7, regardless of anastomotic connections with the common volar digital arteries. A first dorsal metacarpal artery (with either a branch lying superficial to the radial or ulnar head of the first dorsal interosseous muscle, or both branches) and a second dorsal metacarpal artery occurred frequently. A third or a fourth dorsal metacarpal artery was uncommon. Special branches of the princeps pollicis artery anastomosing with the superficial arch that took a similar course to a first dorsal metacarpal artery (Table 4) have not been included here.

D. *Arterial size*

Table 8 shows the mean diameters and relative cross-sectional areas of the major arterial branches and their anastomoses. The ulnar and radial

arteries at the wrist, and the superficial volar arch and the radial artery on the dorsum of the hand were of the same order of size. However, after the origin of the princeps pollicis and volar radial index arteries, the deep arch had a cross-sectional area of less than half that of the superficial arch.

The proper digital, princeps pollicis, superficial volar radial, and median arteries and the deep arch were of the same order of size. So were the anastomotic connections between the common volar digital and volar metacarpal (or volar radial index) arteries and between the superficial volar arch and superficial volar radial artery. Anastomotic connections between the deep ulnar and deep arch, superficial volar arch and princeps pollicis, and between the common volar digital and dorsal metacarpal arteries had somewhat more than half this cross-sectional area.

The dorsal carpal arch and second dorsal metacarpal artery were small, having only one-sixth the cross-sectional area of a common volar digital artery, unless the second dorsal metacarpal anastomosed with a common volar digital artery (when its cross-sectional area was approximately doubled). The first dorsal metacarpal, or its branches, had a cross-sectional area of one twenty-fifth of a common volar digital artery. The other dorsal metacarpal arteries, unless anastomosing with a common volar digital artery, were of similar size to the first. With the exception of the second dorsal metacarpal artery, the entire dorsal arch and its branches were relatively unimportant.

The radial side of the second digit and the ulnar side of the first digit often received a double arterial supply, the former from a superficial volar radial index artery from the superficial arch and from the volar radial index artery from the deep arch, and the latter from the ulnar bifurcation of the princeps pollicis and from a "proper digital" branch of the superficial arch. In both cases there tended to be reciprocal modification in size of either of the two branches concerned. If the superficial volar radial index artery was small or absent, then the volar radial index artery was large so that the total arterial supply remained of the same order as a proper digital artery. The ulnar branch of the princeps pollicis artery had a similar reciprocal size relationship with the branch of the superficial arch supplying the same side of the first digit. However, in the first digit, the ulnarward blood supply exceeded the radialward in a ratio of 4 to $2\frac{1}{4}$ despite the reciprocal size differences.

The volar radial index artery had a cross-sectional area of 1.8 $mm.^2$ and the volar metacarpal arteries, like the dorsal metacarpal arteries, of only 0.8 $mm.^2$ However, when the volar radial index or a volar metacarpal

TABLE 8. MEAN DIAMETERS AND CROSS-SECTIONAL AREAS OF THE BRANCHES AND ANASTOMOSES OF THE ULNAR AND RADIAL ARTERIES (MEDIAN ARTERY, DIAMETER—2.0 MM., CROSS-SECTIONAL AREA—3.0 MM.^{2})

ULNAR BRANCHES	*Diam. (mm.)*	*Approximate cross-sectional area (mm.^{2})*
Ulnar (wrist)	3.5	10
Supf. vol. arch	3.0	7
Common vol. digital	2.5	5
Proper vol. digital	2.0	3
Supf. vol. radial index	1.5	1.8
Supf. ulnar of thumb	1.5	1.8

RADIAL BRANCHES	*Diam. (mm.)*	*Approximate cross-sectional area (mm.^{2})*
Radial (wrist)	3.5	10
Supf. volar	2.0	3
Radial (dorsum)	3.0	7
Dorsal carpal arch	1.0	0.8
1st dorsal metacarp.	0.5	0.2
2d dorsal metacarp. (no anast.)	1.0	0.8
2d dorsal metacarp. (anast.)	1.5	1.8
Princeps pollicis	2.0	3
Princ. poll. ulnar br.	2.0	3
Prin. poll. radial br.	1.5	1.8
Volar rad. index	1.5	1.8
Volar rad. index (to digits 2,3)	2.0	3
Deep volar arch	2.0	3
Volar metacarpal	1.0	0.8

ANASTOMOSES	*Diam. (mm.)*	*Approximate cross-sectional area (mm.^{2})*
Deep ulnar/deep arch	1.5	1.8
Supf. volar arch/princ. pollicis	1.5	1.8
Common volar digit/vol metacarpal	2.0	3
Supf. volar arch/supf. volar (rad.)	2.0	3
Common vol. digit/dors. metacarpal	1.5	1.8

artery anastomosed with a common volar digital artery, its cross-sectional area tended to be increased to the order of a proper digital artery.

In general, the cross-sectional area relations indicated that the first digit and the radial side of the second were supplied by the radial artery and the remaining digital areas by the ulnar artery; but the adjacent sides of the second and third digit often received a major supply from the radial artery either by the volar radial index or by the second dorsal metacarpal artery.

E. *Median arteries* (Table 2)

Median arteries were found in 24 specimens (10 per cent). In most instances they came from the proximal portion of the ulnar artery or from the common or volar interosseous branches and passed down the forearm with the median nerve. In two specimens they arose from the radial artery in the middle of the forearm.

The commonest anastomotic pattern in the 24 hands was UPD, which was present nine times (38 per cent). The main distribution of the median artery in the hands was to all or part of the first two and one-half fingers (19 hands). In 17 hands it anastomosed with the radial artery, in 11 with the ulnar artery, and in four it formed no anastomoses.

In two hands the median and radial artery jointly supplied the first two and one-half fingers, and the ulnar the remaining fingers, but there was no demonstrable anastomosis in the hand between the ulnar artery and the radial-median complex.

F. *Anomalies of the radial and ulnar arteries*

The radial and ulnar arteries of 173 upper extremities were examined. Twenty radial and 16 ulnar arteries were anomalous. The commonest anomaly was high bifurcation of the brachial or axillary artery to form the radial and ulnar arteries. This occurred in 14 specimens (8 per cent), and the bifurcation ranged from the second part of the axillary artery to the lower brachial artery just above the antecubital fossa. In five specimens (3 per cent) the radial artery was formed by the junction at the antecubital fossa of a branch from the axillary or upper brachial artery with a second branch from the normal bifurcation of the brachial. Two ulnar arteries and one radial artery ran down the forearm entirely superficial to the volar antebrachial muscles.

G. *Relationship of the deep branch of the ulnar nerve to the deep volar arch*

The relationship of the deep branch of the ulnar nerve to the deep arch in the depths of the palm was determined in 227 hands. In 113 hands (50 per

cent) the nerve lay posterior to the deep volar arch; in 105 hands (46 per cent) the nerve lay anterior to the deep volar arch. The nerve was distal to the arch in five hands, anterior, then posterior to the arch in two hands, and posterior, then anterior to the arch in two hands.

II. *Comparison of right and left hands*

One hundred corresponding pairs of right and left hands were compared for radio-ulnar anastomoses. The majority of the pairs (79 per cent) were dissimilar. Except for the U *(deep ulnar/deep arch)* anastomosis, which was frequently present in corresponding hands, the number and type of anastomoses in the right and left hands of these 79 pairs varied widely. Twenty-one pairs (21 per cent) had identical radio-ulnar anastomoses. The commonest arrangement was UPD, found in nine pairs of hands.

Seventy-six pairs of hands were examined for similarity of relationship of the deep branch of the ulnar nerve and the deep volar arch. The relationship was the same in both hands in 52 pairs (68 per cent), and differed in 24 hands (32 per cent).

DISCUSSION

The above studies indicate the misleading character of some textbook descriptions of the arterial pattern in the hand. The most impressive feature was the inconstancy of the arteries. This was particularly true of the dorsal and volar metacarpal arteries and the superficial volar branch of the radial. The proper volar digital artery to the radial and ulnar side of each finger was always present, but its origin varied considerably. The proper volar digital arteries to the adjacent sides of the index and middle fingers frequently received an augmented blood supply from the volar radial index and second dorsal metacarpal arteries.

Textbooks often describe the superficial volar arch as being completed on its radial side by anastomosis with the volar radial index or superficial volar branch of the radial artery. However, in this study it was most frequently completed by anastomosis with the princeps pollicis (150 hands), rather than the superficial volar branch (74 hands) or the volar radial index artery (very rarely). The deep arch was more constant, being derived from the deep branch of the ulnar and the palmar continuation of the radial in 94 per cent of the hands. Large anastomoses between common volar digital and volar metacarpal arteries were frequent (56 per cent) but variable.

Some anatomical basis may be offered for the reports of gangrene of the thumb and index finger after interruption of the radial artery at the wrist. In 31 of 250 hands (12 per cent) there was absent or reduced radio-ulnar

anastomosis. Six hands had no demonstrable anastomosis, and 25 had only one, usually by way of a small deep volar arch (17 hands) with an average cross-sectional area of only one-fifth that of either the radial or ulnar artery. The remainder of the hands had two or more anastomoses, which should provide adequate collateral circulation since the smallest average cross-sectional area was almost half that of the radial or ulnar artery. With three or more anastomoses the cross-sectional area was almost equal to, or greater than the 10 mm.^{2} average of the radial or ulnar. The cross-sectional area determinations give only a general relationship of arterial capacity since they do not account for variations in thickness of arterial walls.

The 10 per cent incidence of large median arteries, and eight per cent occurrence of high bifurcation of the brachial or axillary artery are similar to figures previously reported.[3] The nearly equal anterior (46 per cent) and posterior (50 per cent) relationship of the deep branch of the ulnar nerve to the deep volar arch differs somewhat from the 63, 34 per cent incidence reported by Gray.[7]

SUMMARY AND CONCLUSIONS

Two hundred fifty adult cadaver hands were dissected for arterial patterns. Five major types of anastomosis between the radial and ulnar arteries were found in 226 hands, which often differed from common textbook descriptions. The deep branch of the ulnar/deep volar arch anastomosis (U) was found in 94 per cent of the hands, superficial volar arch/princeps pollicis anastomosis (P) in 66 per cent, common volar digital/volar radial index or volar metacarpal (D) in 56 per cent, superficial volar arch/superficial volar branch of the radial (R) in 33 per cent, common volar digital/dorsal metacarpal (M) in 24 per cent, and no anastomosis in two per cent. Twenty-four hands (10 per cent) had median arteries contributing to the blood supply of the hand.

Of the entire group of hands, 88 per cent had more than one of the above types of anastomosis and, on the basis of cross-sectional area calculations in 113 hands, would probably have had adequate collateral circulation if the radial or ulnar artery had been interrupted. Of the various combinations of anastomoses, UP, UPD, UPDR, and UPDRM were the most commonly encountered in 10, 22, 11, and 1 per cent of the total of hands. Twelve per cent had only one anastomosis (25 hands) or none at all (6 hands) and probably had inadequate collateral channels.

The average diameters of the various arteries and anastomoses were determined in 113 hands and their cross-sectional areas were calculated and averaged.

In 173 upper extremities, 20 radial and 16 ulnar arterial anomalies were noted, the commonest anomaly being their formation by a high bifurcation of the brachial or axillary artery (14 arms).

In 226 hands, the deep branch of the ulnar nerve lay posterior to the deep volar arch in 50 per cent and anterior in 46 per cent.

Examination of 100 corresponding pairs of right and left hands revealed similarity in the pattern of anastomoses in only 21 per cent.

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EXPERIMENTAL BACTEREMIA IN NORMAL AND IRRADIATED RATS†

INTRODUCTION

A common finding in animals which have suffered severe radiation injury is invasion of the blood stream by bacilli normally found in the intestinal tract.[1] Accordingly, it is generally conceded that one of the significant aspects of such injury is weakening of the normal barrier which prevents the development of infection by micro-organisms that ordinarily exist harmlessly in the bowel. This bacteremia could be due to one or more of the following: (i) continuous passage of large numbers of bacteria from the bowel into the blood stream, (ii) impaired function of the mechanism which normally effects the removal of bacteria from the circulation, or (iii) escape of a few organisms from the bowel with establishment of infection in other parts of the body and bacteremia as a result of that infection. We are reporting the results of experiments which have a bearing on this subject.

METHODS

The test organism was a strain of *E. coli* originally isolated from urine of a patient with pyelonephritis. It fermented dextrose and lactose, was citrate negative, methyl red positive, Voges-Proskauer negative, indol positive. The organism had been employed in production of experimental pyelonephritis of rats, using the method of Mallory *et al.*,[2] and had been through many animal passages before the present work was done. For these experiments a culture in beef heart infusion broth (Difco) was stored at −20° C. One tube of it was thawed each week and maintained on blood agar base as seed culture for all tests done that week.

The bacterial suspension to be injected into animals was prepared as follows: A small fragment of a colony was dispersed in 5 ml. of beef heart infusion broth and incubated at 37° C. for four hours, then transferred to an ice water bath until needed. The amount injected into an animal was 0.5 ml. The number of viable organisms was estimated in each experiment by making ten-fold dilutions in saline and pouring plates

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at 10^{-6}, 10^{-7}, and 10^{-8} dilutions. The number of colonies per ml. was found to vary between 250,000,000 to 720,000,000, most being between 250,000,000 and 450,000,000.

The rats were Sprague-Dawley strain males obtained from a local supplier. Their weights ranged from 250 to 350 grams.

In most of these experiments the procedure was as follows: Animals were anesthetized by intraperitoneal injection of 12 mg. of pentabarbital sodium, additional doses being given when required. The right femoral artery and vein were exposed below the inguinal ligament, and sterile polyethylene tubes, size PE 50, filled with heparin solution were inserted into the vessels. The plastic tubes were occluded with straight pins which were removed only at time of sampling or injection. Heparin, 0.2 ml., was injected through the venous catheter. The bacterial inoculum was then injected by the same route, and samples of blood for bacterial count were removed via the arterial catheter at suitable intervals thereafter.

In experiments on the course of this bacteremia in normal rats only one blood culture was obtained on each animal. The bacterial suspensions were injected into a tail vein and, at the time for obtaining blood, the animal was anesthetized, the heart was exposed by opening the chest, and the sample aspirated directly from the left ventricle.

The number of bacteria circulating in the blood was determined by conventional pour-plate techniques. Blood samples were diluted immediately in 10-fold increments, 0.5 cc. and 4.5 cc. cold saline. Pour plates were prepared according to the range of bacteremia expected, three dilutions being prepared for each sample of blood. The medium was blood agar base (Difco). The plates were incubated at 37° C. for 48 hours and the colonies were counted, using a Quebec-type counter. The plate in which the number of colonies was more than 30 but less than 300 was taken as giving the most nearly accurate result. In every case, growth was carefully inspected; colonies were checked if suspected of being contaminants, and at least one from every plate was subcultured on Kligler's iron agar and Simmons' citrate agar as a presumptive test to verify presence of *E. coli*.

X-irradiation consisted of 800 roentgens total body exposure (250 k.v.; 15 m.a.; Thoreus filter; 50 cm. distance from the tube) three days preceding the test. This dosage caused profound depression of the number of circulating leukocytes, all animals having total arterial blood leukocyte counts of less than 150 per cu.mm. on the day of study.

RESULTS

Bacteremia in normal rats. In the course of studies related to other problems we have obtained single quantitative blood cultures at various intervals after the intravenous injection of this culture of colon bacillus. These showed an initial bacteremia of one to four million organisms per ml. two to six minutes after the intravenous inoculation. There followed a rapid diminution, so that after 30 minutes the number was generally between one to four thousand per ml. There was often a tendency toward complete clearing at two to six hours, followed by somewhat higher levels at the end of 24 hours, then a decline to negative cultures after 48 hours.

It should be pointed out here that the bacterial inoculation used in this work did not cause discernible infection in normal rats. An occasional animal succumbed within the first 12 hours, probably due either to the anesthetic or to injury by the bacterial endotoxin, but deaths at later periods did not occur. One group of 12 rats was sacrificed 30 days following this inoculation; there had been no sign of illness in them, and cultures of blood, kidney, liver, spleen, and lung failed to yield *E. coli*.

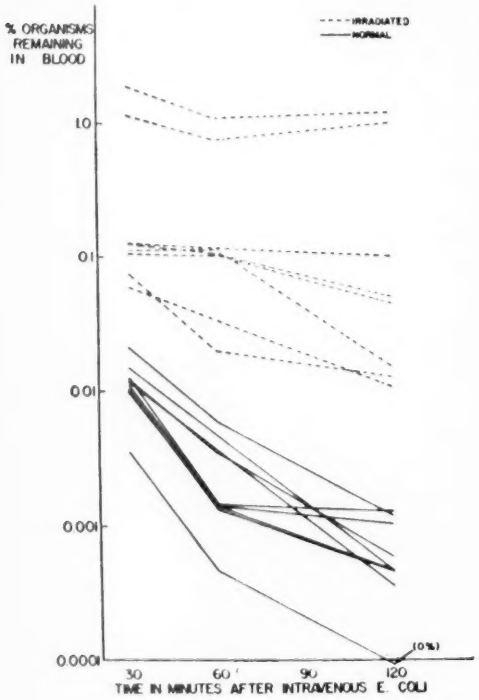

FIG. 1. Removal of *E. coli* from normal and irradiated animals, expressed as percentage of viable organisms injected.

Comparison of bacteremia in normal and in irradiated rats. From the information obtained on bacteremia in normal animals it appeared that the period between 30 minutes and two hours would be suitable for the comparison with irradiated animals. This short test period permitted the obtaining of more than one observation on the same animal and provided an indication not only of the efficiency of initial clearing, but also of any tendency to early development of infection. No attempt was made to lengthen the period of comparison because of the possibility that subsequent development of endogenous bacteremia in the irradiated animals might lead to erroneous conclusions.

Experiments of this nature were carried out on five occasions. Deaths due to hemorrhage during the experimental procedure occurred occasionally, but complete tests were accomplished with nine normal and eight irradiated animals. The colony counts obtained are given in Table 1. The data are also presented graphically in Figure 1 in terms of percentage of

the calculated number of bacteria injected into the circulation of each animal, assuming a blood volume of 20 ml. It will be observed first that there was no great difference in the ability of animals of either group to destroy or rapidly remove the intravenously inoculated bacteria from the blood stream, since only a small fraction of the calculated inoculum could be recovered after 30 minutes. Nevertheless there was a consistent difference between the two groups, in that the counts were higher in the irradiated animals; also there appeared to be less tendency to further reduction during the succeeding 90 minutes in the irradiated animals.

TABLE I. COLONIES PER ML. OF BLOOD IN NORMAL AND IRRADIATED RATS FOLLOWING INTRAVENOUS INJECTION OF LIVING *E. coli*

30 minutes		*60 minutes*		*120 minutes*	
Normal	*Irradiated*	*Normal*	*Irradiated*	*Normal*	*Irradiated*
2,600	8,100	210	11,200	70	1,380
1,600	18,400	240	15,600	60	11,520
1,130	12,500	590	3,700	70	6,900
1,110	14,600	230	12,400	200	2,800
1,840	8,900	70	128,000	80	2,030
1,030	18,600	800	89,000	70	7,400
610	348,000			0	182,000
4,300	161,000			170	110,000
1,720				110	

The data for the 30 minute period were subjected to statistical analysis. Because of the marked difference in variance of the two groups, the "t" test was not suitable. However, a test based on ranks" revealed a highly significant difference (p value less than 0.01).

Second intravenous injection of bacterial culture. The results of the preceding experiments indicated that irradiation did not seriously impair the mechanism which removes micro-organisms from the circulating blood. However, it seemed conceivable that these experiments had imposed about the maximum load on this system and that the different level of bacteremia in normal and irradiated animals was due to exhaustion of the clearing mechanism in the latter group. Another experiment was carried out to test this possibility.

Six rats after being subjected to the usual dose of radiation developed the usual severe leukopenia at the end of three days. An inoculum of 0.5 ml. *E. coli* culture was then given to each one. (The content of this was determined to be 225,000,000 organisms per ml.) After an interval of four

hours, plastic tubes were placed in the femoral arteries and veins and, after drawing blood samples for quantitative culture, a second injection of 0.5 ml. of the same bacterial culture was given into the femoral vein. Subsequent cultures were obtained at 30, 60, and 120 minutes. Three of the six animals succumbed at some stage during the experiment. The results are shown in Table 2. It can be seen that each animal had a positive blood culture before the second inoculum was given, but despite this there was the same efficient clearing of most of the second inoculum within the next 120 minutes. This is interpreted as showing that the clearing mechanism still functions efficiently at this stage of radiation injury.

TABLE 2. TEST OF CAPACITY OF IRRADIATED ANIMALS TO CLEAR A SECOND INOCULUM OF E. COLI FROM THE BLOOD, 4 HOURS AFTER THE FIRST INTRAVENOUS INFECTION OF E. COLI

	Colonies per ml. blood			
Rat No.	*Preliminary*	*30 min.*	*60 min.*	*120 min.*
1	1,270	48,000	*	*
2	8,900	4,200	4,400	2,160
3	71,000	42,000	23,400	21,900
4	80,000	203,000	*	*
5	11,800	12,100	7,600	*
6	880	85,000	39,000	8,100

* Animal succumbed during course of procedure.

DISCUSSION

These experiments were begun in studies of other problems, namely, the pathogenesis of pyelonephritis and the phagocytic function of transfused leukocytes. We are reporting here the results which bear on the problem of the pathogenesis of bacteremia and death following radiation injury.

Many observations on the bacteremia which follows intravenous injection of large numbers of living bacteria in rabbits, dogs, and cats have yielded results comparable with those obtained here in rats. The attention of most investigators seems to have been focussed on the spectacular rapid clearing which takes place within the first 30 minutes. Nevertheless, their results often show, as do ours, that following the initial major removal, a quantitatively less striking bacteremia, i.e., less than 1500 organisms per ml., may persist for 12 to 72 hours, irrespective of the outcome. This does not seem to be due to an exhaustion of the "clearing mechanism," since a second injection of bacteria is followed by the same rapid disappearance of most of the newly introduced organisms within the first 30 minutes. As a matter of

fact, there is little evidence to indicate that ability to clear foreign particles or bacteria from the circulation ever fails, since it has been shown to be functioning efficiently even in moribund animals with massive bacteremia.[1]

Certain possibilities may be suggested in explanation of the low grade bacteremia which persists for 48 hours or more after intravenous injection of a culture of living organisms: (a) It may represent infection of some tissue or tissues, multiplication of bacteria and their discharge into the circulation. This does not seem to be a strong probability in the case of normal animals because, as has already been mentioned, no evidence of infection has been observed in them. (b) It may result from the fact that in the initial clearing of the massive dose of infecting organisms some of them are arrested in certain tissues (e.g., the lungs, voluntary muscle, etc.), but after an interval of time they are again released, to be carried to other organs such as the spleen and liver where they are finally destroyed. This appears to us to be the more probable explanation of the findings in normal animals.

Turning now to the irradiated, leukopenic animals, the most obvious point to be emphasized is that there appears to be no major impairment of "reticulo-endothelial" function, i.e., ability to remove living bacteria promptly from the circulating blood. This is in agreement with the findings of Calloway and Kerby, who reported that bacteria were cleared from the splanchnic circulation of irradiated rabbits.[2]

How are we to look upon the slight but apparently significant difference in level of bacteremia in radiated and normal rats during the period between 30 and 120 minutes? (a) It may be an indication of greater susceptibility of the tissues of irradiated animals to bacterial infection. With the evidence that the clearing mechanism is still efficient in irradiated animals, the fact that they had more bacteria per ml. of blood could be interpreted as evidence that active multiplication of organisms was taking place somewhere, resulting in the entry of large numbers of bacteria into their blood streams. (b) It may reflect diminished ability of the leukopenic animals to destroy organisms wherever they are originally arrested. The studies of Wood[3] show that some of the bacteria which stick to the walls of sinusoids and capillaries are eventually destroyed by the polymorphonuclear leukocytes which also adhere to these areas. From this standpoint it seems reasonable to suppose that granulopenic animals might exhibit a quantitatively greater bacteremia during the period under discussion.

The recent demonstration by Pillemer and associates[5] that properdin, a component of serum protein, plays a rôle in natural immunity to infection, and that properdin is apparently capable of protecting rats against post-

radiation enteric bacterial infection could be incorporated in either of the preceding hypotheses.

SUMMARY

Quantitative blood cultures were obtained from rats following intravenous injection of living *E. coli*. Normal animals were compared with animals which had been subjected to severe radiation injury.

In both groups the main mass of injected organisms disappeared within 30 minutes. There was, however, a consistent and statistically significant difference in number of bacteria remaining in the circulation, irradiated animals having the larger numbers.

Possible causes of the quantitatively greater residual bacteremia in irradiated animals are mentioned. The conclusion is drawn that the principal defect lies not so much in an inability of the fixed phagocytes to extract bacteria from the blood stream as in a lessened capacity to destroy bacteria wherever they are arrested. As a consequence in irradiated animals there is greater opportunity for re-entry of the bacteria into the circulation after temporary sequestration in various locations and for establishment of infection.

* * *

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HEPATIC RADIOAUTOGRAPHY FOLLOWING INTRAVENOUS INJECTION OF RADIOACTIVE CHROMIUM PHOSPHATE AS A FURTHER CONTRIBUTION TO RETICULO-ENDOTHELIAL FUNCTIONAL TESTS§

The complexity of the reticulo-endothelial (RE) functions is reflected in the great difficulties of developing adequate functional tests. Phagocytosis, by definition the characteristic function of the RE system, has served as a basis for most of the functional tests reported.[1] When radioactive colloids were first employed by one of us,[2] this technique was felt to be a very useful tool for studying RE activity. In the course of such studies, however, it was soon discovered that phagocytosis is a very complex phenomenon comprising several independent variables.[3-10] Therefore, further refinement of the technique was needed. At present our routine RE functional tests comprise:

a. *The determination of the phagocytic activity of the total RE system* by measuring the rate of disappearance from the circulation of intravenously injected colloidal radioactive chromium phosphate ($CrP^{32}O_4$).[10] The decrease of the radioactivity in the blood is an exponential function; so a reproducible value for comparison can be obtained by calculating the intravascular "biological half-life" (i.e., the time during which half of the radioactivity is removed from the circulation). This biological half-life value reflects the *over-all* phagocytic activity of the RE system.

b. *The determination of the site of uptake of the test colloid.* Following intravenous administration of $CrP^{32}O_4$ the distribution of radioactivity among the different organs (liver, spleen, kidney, etc.) is very constant in healthy animals.[8] Any distortion of the organ distribution pattern is a sensitive indication of altered RE function. It has been observed that although

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the rate of phagocytosis (i.e., "biological half-life") remained within normal limits in certain experiments, the site of uptake was largely altered. For instance, following whole body x-irradiation[7] or trypan blue pretreatment[8] the compensation of the RE injury is so rapid that the biological half-life remains unchanged or even shorter. Determination of the organ distribution of $CrP^{32}O_4$ reveals, however, extensive RE changes caused by these agents.

c. *The phagocytic capacity of the RE system* can be titrated by injecting increasing amounts of Thorotrast (collodial thorium oxide) and then measuring the degree of the subsequent blockade[9] by determining the "biological half-life" of the $CrP^{32}O_4$. Thus, in case of true hyperphagocytosis[11] a larger dose of Thorotrast is needed to achieve the same degree of blockade as in control animals. In this way small increases or reductions in the phagocytic capacity which are not revealed by testing the phagocytic ability ("biological half-life") can be demonstrated.

The above described triple functional test still left many questions about the complexities of the RE phagocytosis unanswered. Studies on the histological localization of the $CrP^{32}O_4$, using radioautography, provided further information and proved to be a valuable adjunct to the other $CrP^{32}O_4$ tests. The intent of this paper is to describe the technical procedure and outline our interpretation of the hepatic radioautogram following intravenous injection of $CrP^{32}O_4$. Some examples will also be given to illustrate how radioautography may help to interpret the results obtained with the other $CrP^{32}O_4$ tests.

METHOD

Colloidal $CrP^{32}O_4$ suspensions were prepared in the same way as reported before.[10] The anhydrous $CrP^{32}O_4$ was dispersed mechanically in five per cent glucose (concerning particle size, cf. Fig. 1). The animals (mice, rats, and rabbits) were injected intravenously with $CrP^{32}O_4$ and sacrificed one hour later. (Previous studies have shown that even in animals with a considerably reduced phagocytic activity the removal is completed after one hour.) A small piece of liver tissue was fixed in Lavdowsky solution,[18] dehydrated, and, after routine paraffin imbedding, cut in 8-micron-thick sections. Because $CrP^{32}O_4$ is insoluble in water, alcohol, and acids, no dislocation or leaching can occur during the routine histological processing. The mounted (egg white-glycerine) sections were deparafinized, covered with Kodak NT-5 "experimental permeable base stripping film" and exposed usually for a matter of days. (The approximate time was estimated from the number of counts per minute obtained from one specimen.) After exposure, the film was developed for two minutes at 20° C. in Kodak D-19 developer, fixed in Kodak acid fixer for twice the emulsion clearing time, and washed in tap water for one hour. The slide was then stained with either one per cent azure or Giemsa. (Azure had the disadvantage that the color faded

FIG. 1. Electron microscope picture of a routinely prepared chromium phosphate suspension.

FIG. 2. Radioautograms of "normal" rat (A and B) and rabbit (C) livers. Note peripheral lobular localization of radioactivity.

rapidly on exposure to light. The low affinity of the gelatine for this dye, on the other hand, makes it superior to other stains.) In some instances unstained specimens were studied with the aid of phase contrast microscopy with equally satisfactory results. The photomicrograms obtained in this way were perfectly comparable with those from stained sections using regular microscope.

Gross radioautograms were carried out in the following way: dental x-ray film was placed over the deparaffinized section and another glass slide was put on top of the film. The two glass plates were gently compressed with a clamp to secure close contact between the tissue and the film and to avoid sidewise dislocation during the exposure. After the exposure the film was processed in the usual manner for x-ray film.

In all experiments a group of control animals of the same age and sex was added. The histological procedure, exposure time, developing, etc. were kept as identical as possible in the control and experimental groups.

RESULTS

In healthy mice, rats, and rabbits injected with $CrI^{P32}O_4$ a very regular pattern was obtained on the hepatic radioautogram (Fig. 2). The black spots indicate the location of the Kupffer cells containing one or more radioactive particles. The exposed areas are located peripherally along the interstitial septum between the lobuli. (In mice a slight accumulation of exposed spots was observed around the portal veins, see Fig. 3.)

The characteristic peripheral lobular localization of the phagocytized $CrI^{P32}O_4$ particles is plausible considering the liver circulation and the typical histological position of the Kupffer cells as related to the lobular structure of the liver. Figure 4 is a schematic picture of the liver circulation based mainly on the investigation of Elias.[3, 4] The careful histological studies of Pfuhl,[19] recently confirmed by the excellent work of Toro,[20, 21] describe three types of Kupffer cells, which are different in histological appearance and lobular localization. One of them, the characteristic stellate cells (Sternzelle), with elongated cytoplasm straddles the bifurcation of the communicating portal veins (see "C" on Fig. 4). Situated between the two branches at their origin, these cells are optimally exposed to the circulating blood. Pfuhl describes these Kupffer cells as being in a "catching position." Colloidal matter entering the liver circulation first encounters these RE elements around the edge of the lobuli. Obviously this zone of Kupffer cells contains the radioactive particles in our radioautograms.

The other two kinds of Kupffer cells occur along the walls of the sinusoids and at the central vein and are also morphologically different. Pfuhl describes them as being in a "digesting position."

In advanced infectious conditions the hepatic radioautogram showed a markedly distorted pattern. Figure 5 is from a rabbit liver exhibiting

several large and many small abscesses (coccidiosis). The efficient peripheral lobular clearing of the $CrP^{32}O_4$ particles, resulting in a circular distribution pattern in healthy animals, is largely changed due to the infection, and the radioactive particles are almost randomly distributed. It appeared that the distortion of the circular pattern somewhat paralleled the severity of the infection.

Radioautographic studies were very helpful in demonstrating the effect of x irradiation on the RE system. Young, adult, male mice (C57 Strong) were exposed to 100-500 r whole body x irradiation. One day later $CrP^{32}O_4$ was injected intravenously into groups of animals (a) to determine the phagocytic activity (i.e., biological half-life) and (b) for radioautography. In agreement with the findings of others[4] the intravascular biological half-life remained unchanged after the irradiation. The hepatic radioautogram, however, exhibited extensive distortion. In the mice irradiated with the lower doses used, the peripheral removal of the radioactive particles became less efficient (Fig. 6). Many particles have escaped this peripheral filtering zone and can be seen in the sinusoids closer to the central vein. Following 500 r the $CrP^{32}O_4$ particles were scattered in the lobulus without any sign of preferential peripheral localization (Fig. 7).

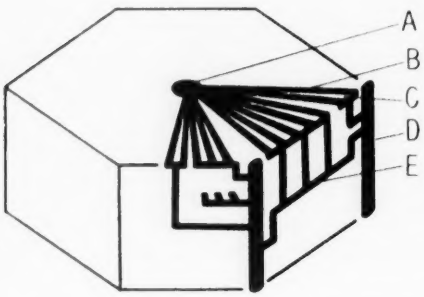

FIG. 4. Schematic diagram of the hepatic lobular circulation. A. Central vein. B. Sinusoid. C. Typical sites of Kupffer cells in "catching position." D. Portal vein. E. Interstitial communicating portal vein.

Attempts to quantitate the radioautographic technique. Odeblad[5] developed a densitometric technique for quantitative gross radioautography. Figures 8 and 9 demonstrate the use of this technique. Rats were injected intravenously with 50 mg. of colloidal iron per kg. body weight. One day later a group of controls was added and the animals were injected with $CrP^{32}O_4$. The hepatic localization of the radioactivity was studied with gross radioautography. Figure 8 is the radioautogram and corresponding densitogram from a control animal. The densitometric scanning was carried out with the photometric device of Odeblad. Briefly, the radioautogram was mounted on a rotating table. The lightsource, placed under the table, was in a fixed position. Above the level of the rotating table a microscope was

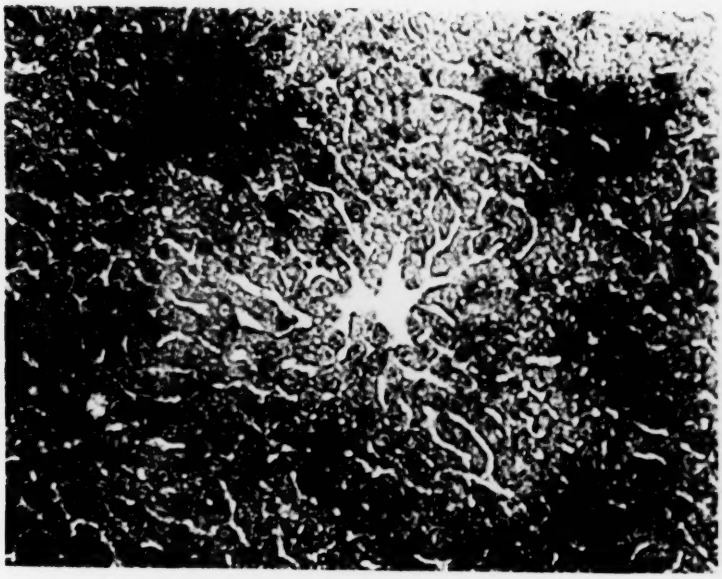

FIG. 4 Radioautogram of "normal" mouse liver

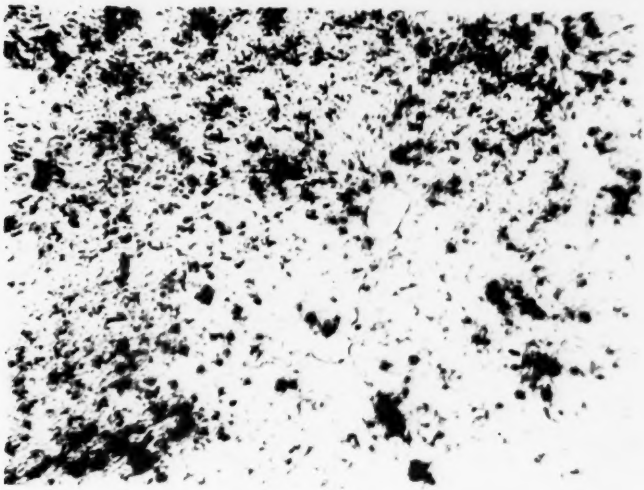

FIG. 5 Hepatic radioautogram of a rabbit with severe coccidiosis. Note lack of preferential peripheral lobular localization of radioactivity

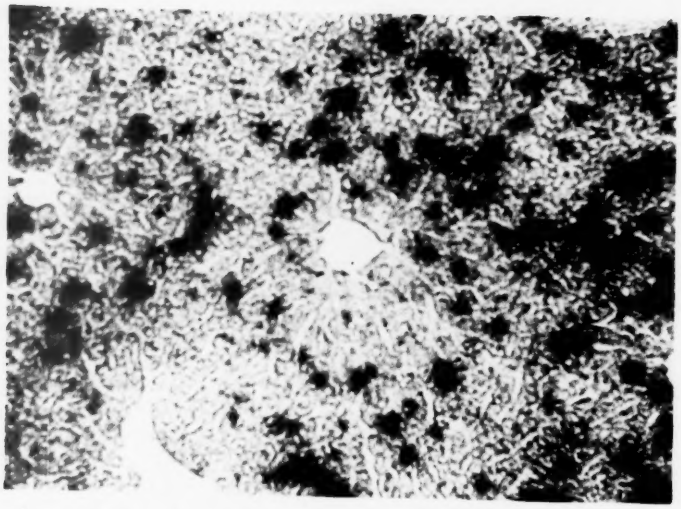

FIG. 6 Hepatic radioautogram from a mouse injected with $CrP^{32}O_4$ one day after 100 r whole body x-irradiation. Note many exposed spots inside the peripheral lobular zone of Kupffer cells (cf. Fig. 3).

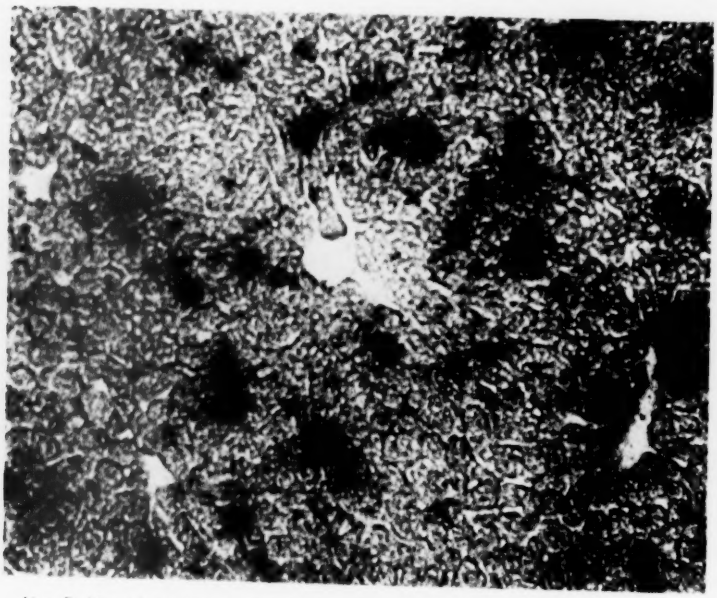

FIG. 7 Hepatic radioautogram of a mouse injected with $CrP^{32}O_4$ one day after 800 r whole body x-irradiation. Note random distribution of radioactivity within the lobulus (cf. Fig. 3) and apparent decrease in number and increase in size of exposed spots. (The same $CrP^{32}O_4$ preparation was used in Figs. 3, 6, and 7.)

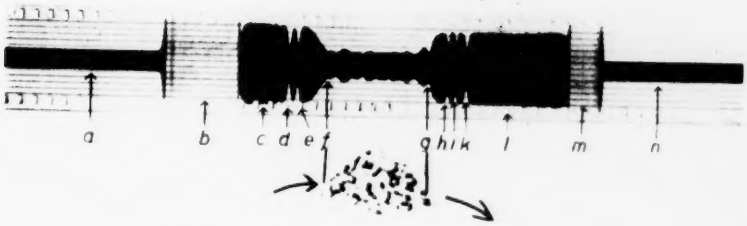

FIG. 8. Radioautogram and corresponding densitogram of a "normal" rat liver section. The arrows indicate the direction and position of the area scanned. On the densitogram:
a and n: instrument reading at complete darkness;
b and m: reading when light source hits the phototube outside the radioautographic film;
c and l: background (fog) of the film;
between f and g: reading across the radioautogram; note the regularity of peaks and valleys.

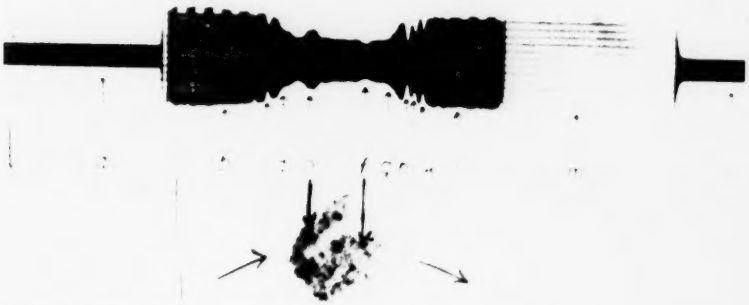

FIG. 9. Radioautogram and corresponding densitogram of a liver section from a rat injected with colloidal iron (ct. text).
a and n: instrument reading at complete darkness;
m: reading when light source hits the phototube outside the radioautographic film;
b and l: background (fog) of the film;
between d and g: reading across the radioautogram; c indicates a blood vessel; note absence of regular peaks and valleys.

mounted; at the level of the image plane of the microscope a diaphragm was built with apertures of different sizes. In our experiments the magnification of the microscope was 1:10 and the aperture 2.0 mm. Therefore, a circular area on the radioautogram with a diameter of 200 μ could be studied. Above the microscope a phototube was mounted which was connected through a modulator and amplifier to a cathode ray oscillograph. Figure 8 shows the results obtained with this technique. The densitogram shows valleys and peaks. The former represents the black spots on the radioautogram, the latter the unexposed areas ("infields" of the lobuli). The distance between two valleys equals the diameter of the lobuli.

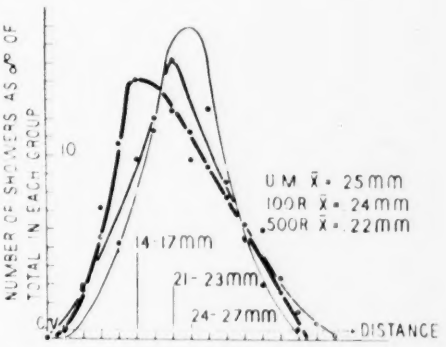

FIG. 10. Frequency distribution of distances between "showers" (exposed spots on the radioautogram) and corresponding central veins in "normal" and x-irradiated mice (cf. text).
U M X represents the mean from the control mice (0.25 millimeter);
100R X represented the mean from mice irradiated with 100 r (cf. text) (0.24 millimeter);
500R X represents the mean from mice irradiated with 500 r (0.22 millimeter); vertical lines along the abscissa mark the groups of highest frequency (0.14-0.17 mm. = 500 r; 0.21-0.23 mm. = 100 r; 0.24-0.27 mm. = control).

Following the pretreatment with colloidal iron, the radioautogram becomes diffuse (Fig. 9) and the circular pattern is scarcely detectable. The densitogram indicates the lack of peripheral lobular distribution by the absence of waves at regular distances obtained in the "control" radioautogram.

The preferential localization of radioactivity in the hepatic radioautogram from healthy animals offers another possibility for semi-quantitating radioautograms. By estimating the average distance of the phagocytized radioactive sources from the central vein of the corresponding lobulus an indication can be obtained concerning the efficiency of the peripheral zone of Kupffer cells. A large number of photomicrograms were taken using adequate magnification so that the field covered a slightly larger area than the lobulus. Only lobuli with the axis perpendicular to the plane of the section were selected. In enlarged prints the distance between each spot (i.e., a Kupffer cell containing one or several $CrI^{332}O_4$ particles) and the center of the lobulus was measured. Figure 10 demonstrates some of the results obtained. In this experiment (57 Black

mice were exposed to whole body x-irradiation. The dose used was between 100 and 500 r. Next day a group of untreated animals of the same litter was added and all mice were injected intravenously with the same $CrP^{32}O_4$ preparation. What is so apparent by mere inspection (Figs. 6-7) can be verified by this method of evaluation. X-irradiation reduced the "average distance" considerably and the shape of the frequency distribution curve became distorted also. While in the controls a normal distribution curve was obtained, in animals irradiated with 500 r the distribution curve became askew (obviously the left side of the distribution curve cut off by the presence of the central vein).

Another way of comparing the different radioautograms is to count the number of exposed black spots over each lobulus and compare the number of v. Kupffer cells containing radioactive particles in control and experimental animals. We have found that whole body x-irradiation not only interfered with the localization but also reduced the number of v. Kupffer cells containing radioactive particles. Following 100 r whole body x-irradiation this reduction amounted to 24 per cent, and 500 r diminished this number to 43 per cent in C57 Black mice when tested 12 hours after the irradiation.

DISCUSSION

The main observation described in this paper is the characteristic radioautographic pattern in the liver, obtained consistently after intravenous administration of our $CrP^{32}O_4$ preparations. Although similar trends in the localization of phagocytized colloidal matter have been noted by others, the reproducibility of this phenomenon and its distortion under experimental conditions has not been emphasized. The radioautograms presented by Vekerdi *et al.*[22] resemble very much the pattern we obtained in our studies. Pfleger and Frimmer[18] observed that following the intravenous injection of colloidal polyphosphate localization decreased towards the central vein. The amount of colloidal matter injected was, however, much higher (7 mg.) than in our studies. Probably the Kupffer cells of the peripheral zone became saturated. Therefore some of the material was taken up deeper in the sinusoids.

The densitometric technique of Odeblad seems to add little to the evaluation of the radioautogram. Further refinement would be needed to increase the resolving power of this technique. The other two methods tried, i.e., the "average distance" of the radioactive particles from the center of the lobulus and the "average number" of Kupffer cells containing

$CrP^{32}O_4$ per lobulus gave us better quantitative data for comparing the findings in various experimental conditions. This way of quantitating radioautograms contains a number of sources of error. Some of these are: the $CrP^{32}O_4$ preparation contains a broad spectrum of particle sizes, ranging from around 0.01 micron to several microns (Fig. 1). The size of the $CrP^{32}O_4$ particle, and consequently their P^{32} content, exhibits a great variability. Therefore the size and the degree of the black spots varies considerably. Bearing this in mind we overexposed our radioautograms deliberately in order to get intensive blackening over even small individually phagocytized particles. (Often in case of RE impairment, e.g. following irradiation without overexposure, one would overlook those small particles which are often deeper in the infield of the lobulus.) In such overexposed radioautograms the radiation originating from several different, but proximate Kupffer cells may produce large confluent "sunbursts." This will give false values when counting the number of spots per lobulus. This error could be overcome by reducing the exposure time. In this case one might look for an aggregation of exposed silver granules as the beginning of an exposed "spot," thus increasing the resolving power of technique. We preferred the overexposed radioautograms because these gave a better overall picture under low magnification, which seemed to be desirable for evaluating the preferential localization of the phagocytized particles as related to the lobular structure.

The method, of course, comprises all the errors of a histological technique. (Variability of the thickness of the section, shrinkage of the tissue during processing, etc.) The distance between the particle and the film also affects sharpness of the exposed spot. Absorption and scattering increases with the distance between the radiation source and the film. The backscattering from the glass slide also contributes to the errors. The importance of these factors became very apparent when attempts were made to stain the section prior to the radioautographic procedure. The mounted and stained sections were coated with a thin layer (less than 1 micron) of lacquer and then covered with the stripping film. When these results were compared with those without the lacquer coating, it was obvious that the radioautograms were misleadingly distorted due to the presence of the lacquer. The small individually engulfed particles did not cause an intensive enough exposure of the film, and the over all picture showed only a few big lakes of sunbursts.

Whereas the quantitative aspects of the radioautographic technique still could be improved, the method seems to provide us with valuable information, especially in certain experimental conditions when the other $CrP^{32}O_4$

methods fail to register unequivocally the changes in RE functions, as was the case following pyrogen injection of rabbits[12] or whole body x irradiation.[9]

Beyond the use of radioautography as a further adjunct to the $CrP^{32}O_4$ technique, an important conclusion can be drawn from the above reported result with regard to the *functional inhomogeneity* of the RE elements in the liver. Following intravenous administration, about 70-85 per cent of the $CrP^{32}O_4$ (depending on the particle size[8]) will be phagocytized by the liver. Consequently, the rate of disappearance of the radioactivity from the blood (i.e., intravascular half-life) will be mainly determined by (a) the liver circulation, and (b) the efficiency of the peripheral lobular zone of the Kupffer cells. Using other colloids for testing, which will be phagocytized with evenly good chances by all the Kupffer cells of the liver, different results might be obtained. The colloids used apparently by Frimmer, Vekerdi, and by us are mainly concerned with the peripheral zone of the Kupffer cells, while others using certain preparations of radiogold, India ink, etc., might test the entire phagocytic system of the liver. Therefore it is necessary to qualify an RE functional test by checking with radioautography or regular histology the hepatic localization of the injected colloid. Histological studies appear to be of great importance in order to clarify contradictory results, because other experiments of this laboratory strongly suggest a functional difference among the various RE elements of the liver, e.g. in immune response. The peripheral zone of Kupffer cells is apparently very radioresponsive, cortisone sensitive, and certainly involved in immune response. Further careful studies are needed to clarify the rôle on the "infield" RE elements in these processes.

SUMMARY

A detailed description of the radioautographic technique used has been given. Following intravenous injection of colloidal chromium phosphate containing P^{32} the radioactive particles were demonstrable only in the peripheral zone of Kupffer cells along the interlobular septum in liver. Examples were given where this characteristic distribution of the phagocytized material was altered, such as infection and whole body x-irradiation. Some methods for semi-quantitating the radioautographic findings are described. The usefulness of the technique has been discussed and the anatomical and probably functional inhomogeneity of the reticulo-endothelial elements in the liver pointed out.

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BOOK REVIEWS

TEXTBOOK OF PHYSIOLOGY. John F. Fulton, Ed. Philadelphia, W. B. Saunders & Co., 1275 pp. $13.50.

This 17th edition of what was originally Howell's textbook appears six years after its predecessor. Certain portions have been extensively modified and new chapters have been added, though the over-all length remains the same. The general outline and approach are unchanged, and the principal changes only will be considered here. Most sections have been brought carefully up to date.

The reviewer missed the opening chapter of the older edition, a historical introduction by Dr. Fulton. The first seven chapters on neuronal mechanism have been slightly expanded, and considerable new material on electrical and metabolic interrelationships has been added. Later in the text is a fresh chapter on acetylcholine and energy transformation in nerve cells. It would seem that these might have been brought together.

The section on muscle includes a welcome expansion of information on molecular mechanisms.

The treatment of the central nervous system is notable for a new chapter on the limbic system with an excellent and recent bibliography. The section on sensation is little changed except for a new chapter, "Pathophysiology of Pain," and the inclusion of new experimental data on electroencephalography.

The chapter on blood clotting, felt by the reviewer to have been a weak spot in the previous edition, has been well rewritten by a new author, Dr. Rosemary Biggs. Electrocardiography has been set off in a separate chapter and expanded to include data on body surface equipotentials.

Respiratory regulation has been rewritten by Drs. Breckenridge and Hoff, on the basis of their own extensive investigations. Body fluids and the kidney have also received a new treatment under the editorship of Dr. William Blake.

The high standard of writing and editing is maintained throughout. The bibliographies are longer and for the most part up to date, though the citations no longer include the titles of papers. The format has undergone only minor changes. The index appeared adequate when searched for topics in the reviewer's particular interests.

W. P. MCNULTY, JR.

THE TUBERCLE BACILLUS IN THE PULMONARY LESION OF MAN. By Georges Canetti. Foreword by Rene J. Dubos and Walsh McDermott. New York, Springer Publishing Co., Inc., 1955. 226 pp. $8.50.

This small but scholarly volume is dedicated to the integration of histopathological and bacteriological knowledge of tuberculosis in man. As is stated in the foreword, Dr. Canetti's approach to the study of pathogenesis is refreshingly simple. The first chapter presents an excellent and readable review of the histopathology of tuberculosis. In the second chapter an attempt is made to correlate the number of tubercle bacilli seen in tissue sections with the various types of histopathology. It is shown that certain

lesions tend to have relatively large numbers of tubercle bacilli present, whereas others tend to have very few. However, the variations in the number of bacilli found in any one type of lesion is often so great that the average does not give a true picture of the situation. In one instance, for example, a series of 19 lesions were studied in which the bacterial content varied from 0 to 20,000 per hundred fields; the average of 8,000 bacilli does not convey any meaning. One would raise the question as to whether the figures presented in this chapter are statistically significant.

Chapter 3 is devoted to the histobacteriogenesis of tuberculous lesions and a comprehensive discussion of the numerous factors which affect this process. An attempt is made here to solve the vexing problem of the viability of organisms which can be seen in tissue. The author uses the technique of counting organisms seen in a tissue section and comparing this number with the number of colonies found on culture of a similar section. The validity of this approach is probably open to some question since the percentage of positive growth depends largely on the cultural technique employed. To assume that every viable bacillus will produce a colony on culture would assume that our cultural techniques are 100 per cent perfect. That this is far from true is attested to by the various reports in the literature which show a wide variation in the percentage of positive cultures which various authors are able to produce. It has recently been shown by Gladys Hobby, for example, that the percentage of positive cultures from tissue specimens can be greatly increased by special cultural techniques and longer periods of incubation.

Chapters 4 and 5 discuss, respectively, the tuberculous lesions and immunity, and the relation of the tuberculous lesion to the therapy of tuberculosis. Both of these chapters make extremely interesting and informative reading. As is his method throughout the entire book, Dr. Canetti observes the problems from many different angles, discusses numerous possibilities, and raises many questions. He closes with a note of warning that chemotherapy is unlikely ever to become the exclusive treatment of pulmonary tuberculosis, emphasizing the fact that up to the present time, the most successful treatment has been a combination of chemotherapy and other factors of long established value, and pointing out that chemotherapy has as yet been of little value in the caseous lesion.

This book is well worth reading in that it provides an excellent review of the basic science of tuberculosis while raising many stimulating and provocative questions. For the clinician it will be a sobering influence and a reminder that a modicum of therapeutic success has not solved all the problems in the field of tuberculosis.

NORMAN L. CRESSY

OUTLINES OF ENZYME CHEMISTRY. By J. B. Nielands and Paul K. Stumpf. New York, John Wiley and Sons, 1955. x, 315 pp. $6.50.

This book offers to the early student of biochemistry and research worker in other fields a guide to basic principles and currents in the field of enzymology. It is written with clarity and directness and illustrated with

many formulae and figures. Its many chapter subheadings give the book its rather terse, outline form.

A discussion of methods of isolation, characterization, and determination of purity is followed by successive chapters dealing with reaction rates as a function of substrate concentration, inhibitor action, temperature, and pH. Thermodynamic concepts are well developed in chapters on energetics and oxidation reduction. The problem of the mechanism of enzyme action is presented in chapters on enzyme-substrate compounds and enzyme specificity.

Following these sections on the basic principles of enzyme chemistry, which take up half the book, the authors treat the chemistry of coenzymes and the classification of enzymes. An especially good treatment of respiratory enzymes is given. The remainder of the book deals with metabolic pathways. Insofar as the book is intended for students thoroughly grounded in biochemistry, it is likely that this section will come as unnecessary repetition either as reading or in a course dealing with enzyme chemistry. However, an added chapter contributed by Roger Stainier on the problem of enzyme synthesis as interpreted from induction experiments is a welcome addition to textbook literature in biochemistry.

If nothing else, the more than 650 references to important articles and reviews make this book an excellent up-to-date survey of the literature as well as a good introduction to the numerous polygraphs now available in enzymology.

IRWIN A. ROSE

THE HYPOPHYSEAL GROWTH HORMONE, NATURE AND ACTIONS. An International Symposium sponsored by the Henry Ford Hospital and Edsel B. Ford Institute for Medical Research, Detroit, Michigan and held at the Hospital, October 27, 28, 29, 1954. Richmond W. Smith, Jr., Oliver H. Gaebler, and C. N. H. Long, Eds. The Blakiston Division, McGraw-Hill Book Company, Inc., 1955. xv, 570 pages; tables, figs., plates.

This book contains the complete proceedings of a symposium on growth hormone held at a time when study of this pituitary principle holds the attention of many. Eminent workers in the field participated and described their most recent physiological, biochemical, and physiochemical studies. This fine book is notable for the comprehensiveness of its information and the many new ideas presented. The discussions, vigorous but coherent, greatly enhance the value of the formal contributions. Because the studies on growth hormone have spread so wide, a summary of the contents may bring to the attention of those not specializing in the field aspects that concern them.

The first part of the symposium is devoted to bioassay and physiochemical properties. A partial chemical structure is presented; important biological and physiochemical differences are found in growth hormone from various species. In Part II, the emphasis is on morphology, including growth hormone action on the glands of the digestive system, kidney, skeleton, and connective tissue. The limitations of growth hormone, effects of over-dosage, and relation to the actions of other hormones are discussed.

Parts III and IV deal with the actions of growth hormone in fat, nitrogen, and carbohydrate metabolism. The actions of pancreatic and adrenal hormones in these systems are related to and contrasted with those of growth hormone, resulting in a wide coverage of hormonal influences on metabolism. The work is at a level where the fundamental mechanisms of action can be discussed in terms of individual enzyme systems. These middle sections are in many ways the heart of the symposium. With a necessary scepticism, some speakers suggested that the purest growth hormone preparations might contain more than one active principle, a problem for future work to resolve. In Part V are collected the papers on the influence of growth hormone on the mammary gland and the effects of all endocrine factors reviewed. To complete the symposium there are two papers concerning the administration of growth hormone to humans. The paucity of the clinical information to date is disappointing, but the good evidence that growth hormone holds a central position in the regulation of many body processes will surely inspire further work. The intention of the sponsors of the symposium was to advance basic research; through the medium of this symposium report their aims will be well served.

M. STACK DUNNE

FOURTH ANNUAL REPORT ON STRESS. By Hans Selye and Gunnar Heuser. Montreal, Acta Inc., 1954. 749 pp.

For the past five years, Selye has annually published an annotated bibliography on "stress," including biological, experimental, clinical, and theoretical papers. Since the stressing influences ("stressors" in the jargon of the cult) include almost all environmental, bacteriological, chemical, and psychiatric influences to which an organism may be exposed, and since adaptation to the "stressor" may include endocrine, immunologic, vasomotor, inflammatory, and enzymatic changes, the only limit to the size of the bibliography is the energy of the author. The bibliography proper is immense, occupying 151 pages; access to this mass of literature is provided by a 240 page outline in which the interreactions of the stressors and stimuli with the various targets are set forth. Interpretation of this outline requires mastery of a set of instructions and a glossary of terms and abbreviations which occupies seven pages. For the reader interested in meeting "stress" in Selye's terms, the combination of outlines and bibliography represents a valuable tool.

Most of the remainder of the book is occupied by a series of essays by Selye. These include a review of the development of the "stress" concept, an introduction to experimental design for the study of "stress," afterthoughts on an integrated system of medicine (the first thoughts were outlined in the 1953 edition), philosophical discussions of homeostasis, endocrinology, and the newly introduced "local adaptation syndrome."

Ten separate authors have also contributed articles, which vary in length from a one-page table by Brochner-Mortensen on the treatment of rheumatoid arthritis with cortisone to a 35-page monograph on "Nutritional Endocrinological Interrelationships in the Pathogenesis of Hypertension and Atherosclerosis over the Life Span" by Stamler, Katz, and Pick. These

essays represented the most stimulating part of the book to this reviewer. I was particularly interested in the papers by Simpson and Tait on Aldosterone and the one by Harris and Fortier on the regulation of the release of ACTH. All of the essays are useful, but their contents have appeared in previous reviews elsewhere, often by the same authors; indeed, Moore's paper on "Bodily changes in Surgical Convalescence" is merely a reprint of a paper which appeared in 1953 in Annals of Surgery, slightly modified to bring it up to date.

The Fourth Annual Report on Stress (AROS, 1954, in the Selye shorthand) is, therefore, likely to appeal chiefly to those workers who have patterned their thinking on Selye's hypotheses. For readers who prefer to work out their own medical cosmogeny the main interest of the book will probably lie in the reviews it contains.

PHILIP K. BONDY

LEUKOCYTIC FUNCTIONS. Roy Waldo Miner, Ed. Annals of the New York Academy of Sciences, Vol. 59, Art. 5, pp. 664-1070. New York, 1955.

Early this year a conference on leukocytic functions held at the New York Academy of Science was dedicated to Dr. Hal Downey. Twenty-six papers were presented by a group of outstanding hematologists, and these have been bound together in a four-hundred-page manual. The entire collection of papers presents not only a very comprehensive review of leukocyte function but also a considerable amount of current investigative data. Many well reproduced tables, charts, and photographs as well as an extensive bibliography have been included. The manual is of sufficient detail to be of interest, principally, to hematologists, but it should function as an excellent reference to those interested in any aspect of leukocyte normal or pathologic physiology.

STUART C. FINCH

THE COLON: ITS NORMAL AND ABNORMAL PHYSIOLOGY AND THERAPY. Annals of the New York Academy of Sciences, Vol. 58, Art. 5, pp. 664-1070. New York, 1955. $4.50.

This paper-bound volume is stated to be the "result of a conference" held at the New York Academy of Sciences in May 1953. It contains twenty-three articles about the lower bowel which range from the effects of early bowel training on colonic function to an earnest discussion of the merits of "caroid and bile salts." Its uneven repetition of much that the participants have published elsewhere makes one question the wisdom of the present-day trend of publishing the results of conferences. Such a conference would seem to be of more value for the private than for the written word. At any rate, there is a massive amount of repetition from article to article that should have been eliminated.

Several sections, however, are well worth reading: the one on the physiology of the colon is particularly noteworthy. The etiology of colonic disorders is discussed from many aspects, from the congenital to the psychological. A warning by Dr. Edward Kempf seems particularly appropriate

in this regard, "You have this problem: What does the situation mean to the patient, not what does the situation mean to you? On this rock founders many a carefully planned study related to fear, anger, security, and the other cliches of colonic language.

A longish section on the effect of cathartics summarizes much information of which the reviewer was unaware, but leaves open the question of how often laxatives really are necessary. It is difficult to take seriously an ingenious statistical study of laxatives that evaluates the average number of bowel movements in terms of 7.865 movements per 10 days.

The therapeutic section is highlighted by Dr. White's and Dr. Machella's discussions of ulcerative colitis and by Dr. Inglefinger's advice on constipation. The general reader will enjoy browsing through this book.

HOWARD M. SPIRO

RESERPINE IN THE TREATMENT OF NEUROPSYCHIATRIC, NEUROLOGICAL, AND RELATED CLINICAL PROBLEMS. Roy Waldo Miner, Ed. Annals of the New York Academy of Sciences, Vol. 61, Art. 1, pp 1-280. New York, 1955. $3.50.

Out of the mystical folklore of India into the medicine cabinets of psychiatric wards throughout America comes Reserpine, the potent alkaloid extracted by our enterprising drug industry from the potent herb Rauwolfia serpentina. Accompanied by publicity rivaling that given to cortisone, Kinsey's books, and the Salk vaccine, this drug is being promoted as the probable answer to the problems of mental illness, crotchety old age, colicky infancy, and diverse physiological disorders.

In order to assess the reports of the many investigators engaged in studying this drug and others like it, symposia are held here and there from time to time. The studies, many of them sponsored by the drug houses, frequently are presented with remarkable unanimity of successful findings and optimistic conclusions.

Such a conference was held on April 15, 1955 by the New York Academy of Sciences and the papers presented have been published in a 280-page paperback volume. Thirty studies are presented of which seven report on neuropharmacological effects of reserpine on animals and humans. The remaining twenty three articles are clinical studies reporting the effects of reserpine on patients with various diseases and disorders.

The neuropharmacological papers are impressive in their design, thoroughness, and findings. They demonstrate that reserpine by specific and general action on the central and autonomic nervous systems facilitates cortical regulatory mechanisms and produces parasympathetic predominance. Behaviorally this results in reduction in psychomotor activity, so that tranquilization without sleep is produced. Also, hypotension and apparently reversible systemic side effects occur, including a Parkinson-like syndrome. The drug is of low toxicity, and seems to have great promise as a means of calming agitated, hyperactive, and hypertensive patients. Its greatest usefulness so far has been in converting night marish back wards in mental hospitals into quiet and peaceful wards of drugged but tranquilized patients. It is

uncertain, however, whether or not even this usefulness is more for the needs of the staff and administrators of these wards than for the needs of the patients in them. The drug does not seem to affect ideation or basic psychopathological processes.

The twenty-three clinical papers deal with the effect of reserpine on the clinical course of psychoses, neuroses, headache, narcotics withdrawal, brain trauma, epilepsy, and skin disorders. All report favorable results but controls are usually poor, follow-up frequently absent, and conclusions often unwarranted from the data. The enthusiastic reports of the curative effects of reserpine on patients with psychiatric disorders are reminiscent of the unfulfilled claims made in the past for the efficacy of insulin coma, electroshock, lobotomy, hormone and carbon dioxide therapies. However, both the low toxicity and the calming effect of the drug are confirmed by all the studies.

This publication is recommended as being informative for those readers who want to find out about reserpine, or who are interested in neuropharmacology, or who are as yet unaware of the unscientific standards of clinical research frequently reported in modern psychiatry, particularly by those who advocate "pills for the mind."

LOUIS B. FIERMAN

NEUROPHARMACOLOGY. TRANSACTIONS OF THE FIRST CONFERENCE, May 26-28, 1954. Harold A. Abramson, Ed. New York, Josiah Macy, Jr. Foundation, 1955. 210 pp. $4.25.

This publication is a presentation of the Transactions of the First Conference on Neuropharmacology held in May 1954. The importance of this field is emphasized in the stimulating introductory statement of Ambassador William Borberg, delegate of Denmark to the United Nations, who discussed the significance of the study of the neurological and psychological effects of drugs in relation to the social setting. The participants then reviewed certain specialized aspects of the total field. The usual verbatim accounts typical of the Josiah Macy Conference Series were reported with all the benefits and shortcomings of this method of publication.

The first two papers may be considered basic in that they present first, considerations of the effects of pharmacological agents on the over-all circulation and metabolism of the brain by Seymour S. Kety, and second, the functional organization of the brain by Ernest A. Scharrer. Kety's extensive material is concerned with the methods of determining the over all circulation and metabolism, and the effects of many drugs, hormones, and other procedures such as ganglionic block and inhalation of oxygen and carbon dioxide. The fruitful discussion provided a thorough and valuable critique of the limitations of the methods with indications for further investigation. A very complete reference list is appended in this section.

The material on functional organization of the brain was particularly concerned with certain cytological aspects, especially the distribution of enzymes ("chemoarchitectonics"). The hope was raised that the selective action of some drugs may be correlated with the localization of certain

enzymes. Also, the problems of local circulation and capillary distribution were considered in relation to vulnerability of certain areas, i.e., Ammon's horn.

The remaining three papers presented material concerned directly with pharmacological studies. These were: studies of the electrical activity of the brain in relation to anesthesia by Mary A. B. Brazier, the ascending reticular system and anesthesia by Horace W. Magoun, and observations on new central nervous system convulsants by Carl C. Pfeiffer. The first two papers reviewed mainly the electrical aspects of the effects of anesthesia. Brazier presented in detail the various electroencephalographic changes that occur under anesthesia especially with barbiturates, showed some of the differences between surface and depth recording, and the electrical responses to sensory stimulation, especially photic. Magoun emphasized the ascending reticular formation in the brain stem concerned with the electroencephalographic arousal reaction as the pathway involved in general anesthesia rather than the classical somatic afferent sensory pathways. The "reticular route" to the cortex is regarded as quite susceptible to anesthetic agents because of its multisynaptic organization.

The report on new CNS convulsants by Pfeiffer included a presentation of two interesting new drugs. One, acridone, is fluorescent and its distribution in the nervous system may be studied after administration. The other, one of a group of convulsant hydrazides has a well defined action, being convulsant by virtue of inducing a pyridoxine deficiency. It is hoped that further studies of these drugs might develop information concerning the metabolic basis of neuronal excitability. In the discussion of this material there was brief reference to the effects of hormones on central nervous system function and the psychological effects of lysergic acid or LSD 25. It should be noted that table 10 is presented quite out of place between pages 80 and 81, belonging rather between pages 182 and 183.

This conference, therefore, primarily considered certain introductory, basic aspects in the field of neuropharmacology and only two special drug effects, the anesthetic and the convulsant. This field is becoming increasingly wider and more significant, and it is hoped that in further conferences other problems will be considered, especially those concerning anti convulsants, drugs involved in neuromuscular transmission, drugs affecting the autonomic nervous system, and finally the drugs and other substances such as hormones which produce definite psychological effects such as the adrenal steroids, mescalin, LSD 25, the Rauwolfia substances, and chlorpromazine. This present volume is recommended as an introduction and initial critique and it is hoped that the future conferences will uphold this first standard.

GILBERT H. GLASER

ADVANCES IN VIRUS RESEARCH. Vol. II. K. M. Smith and M. A. Lauffer, Eds. New York, Academic Press, 1954. 313 pp. $7.00.

For a single reviewer to attempt a critical evaluation of all of the papers in this volume would indeed be presumptuous, for each is written by an expert who is thoroughly familiar with his subject. Assuming that the

reviewer is omniscient, however, a critical review in order to be fair to each contributor would have to be unduly long. Thus a listing of the authors and their subjects should suffice to indicate the great value of this collection, especially when it is considered in conjunction with that of the first volume: Inheritance of resistance to viral diseases in plants, Francis O. Holmes; Inhibitors and plant viruses, F. C. Bawden; Incomplete forms of influenza virus, Preben von Magnus; Characteristics of viral development in isolated tissues, W. Wilbur Ackermann and Thomas Francis, Jr.; The action of ionizing radiation on viruses, Ernest Pollard; The chemical constitution of viruses, C. A. Knight; Electron microscopy of viruses, Robley C. Williams; The hydration of viruses, Max A. Lauffer and Irwin J. Bendet.

There is no doubt that the aim of the editors, Kenneth M. Smith and Max Lauffer, "that, as the volumes accumulate, the reviews appearing in *Advances* will provide the individual scholar with the material he needs to synthesize his own view of virology as a whole" is being brought to fruition by the excellence of the material presented in Volume II.

LISBETH M. KRAFT

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